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Artículos originales (todos) \*\*\* Original articles (all)

Cancer Pharmacogenomics.

Abril - Mayo 2013 / April - May 2013

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[1]

**TÍTULO / TITLE:** - Phase III Randomized, Placebo-Controlled Study of Cetuximab Plus Brivanib Alaninate Versus Cetuximab Plus Placebo in Patients With Metastatic, Chemotherapy-Refractory, Wild-Type K-RAS Colorectal Carcinoma: The NCIC Clinical Trials Group and AGITG CO.20 Trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 20.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.46.0543](#)

**AUTORES / AUTHORS:** - Siu LL; Shapiro JD; Jonker DJ; Karapetis CS; Zalcborg JR; Simes J; Couture F; Moore MJ; Price TJ; Siddiqui J; Nott LM; Charpentier D; Liauw W; Sawyer MB; Jefford M; Magoski NM; Haydon A; Walters I; Ringash J; Tu D; O'Callaghan CJ

**INSTITUCIÓN / INSTITUTION:** - Lillian L. Siu, Malcolm J. Moore, and Jolie Ringash, Princess Margaret Hospital and University of Toronto, Toronto; Derek J. Jonker, The Ottawa Hospital and the University of Ottawa, Ottawa; Nadine M. Magoski, Dongsheng Tu, and Chris J. O'Callaghan, National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Ontario; Felix Couture, Centre Hospitalier Universitaire de Quebec Pavillon Hotel Dieu de Quebec, Quebec City; Danielle Charpentier, Hopital Notre Dame, Montreal, Quebec; Jehan Siddiqui, Dr H. Bliss Murphy Cancer Centre, St John's, Newfoundland; Michael B. Sawyer, Cross Cancer Institute, Edmonton, Alberta, Canada; Jeremy D. Shapiro, Cabrini Hospital and Monash University; John R. Zalcborg and Michael Jefford, Peter MacCallum Cancer Centre and University of

Melbourne; Andrew Haydon, Alfred Hospital, Melbourne; Chris S. Karapetis, Flinders Medical Centre and Flinders University; Timothy J. Price, The Queen Elizabeth Hospital and University of Adelaide, Adelaide; John Simes, National Health and Medical Research Council Clinical Trials Centre, University of Sydney; Winston Liauw, St George Hospital and University of New South Wales, Sydney; Louise M. Nott, Royal Hobart Hospital, Hobart, Australia; and Ian Walters, Bristol-Myers Squibb, Wallingford, CT.

**RESUMEN / SUMMARY:** - PURPOSE The anti-epidermal growth factor receptor monoclonal antibody cetuximab has improved survival in patients with metastatic, chemotherapy-refractory, wild-type K-RAS colorectal cancer. The addition of brivanib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor and fibroblast growth factor receptor, to cetuximab has shown encouraging early clinical activity. PATIENTS AND METHODS Patients with metastatic colorectal cancer previously treated with combination chemotherapy were randomly assigned 1:1 to receive cetuximab 400 mg/m<sup>2</sup> intravenous loading dose followed by weekly maintenance of 250 mg/m<sup>2</sup> plus either brivanib 800 mg orally daily (arm A) or placebo (arm B). The primary end point was overall survival (OS). Results A total of 750 patients were randomly assigned (376 in arm A and 374 in arm B). Median OS in the intent-to-treat population was 8.8 months in arm A and 8.1 months in arm B (hazard ratio [HR], 0.88; 95% CI, 0.74 to 1.03; P = .12). Median progression-free survival (PFS) was 5.0 months in arm A and 3.4 months in arm B (HR, 0.72; 95% CI, 0.62 to 0.84; P < .001). Partial responses observed (13.6% v 7.2%; P = .004) were higher in arm A. Incidence of any grade  $\geq$  3 adverse events was 78% in arm A and 53% in arm B. Fewer patients received  $\geq$  90% dose-intensity of both cetuximab (57% v 83%) and brivanib/placebo (48% v 87%) in arm A versus arm B, respectively. CONCLUSION Despite positive effects on PFS and objective response, cetuximab plus brivanib increased toxicity and did not significantly improve OS in patients with metastatic, chemotherapy-refractory, wild-type K-RAS colorectal cancer.

[2]

**TÍTULO / TITLE:** - Inhibitors of rogue enzyme near trials for brain and blood tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nat Med. 2013 May;19(5):514. doi: 10.1038/nm0513-514.

●●Enlace al texto completo (gratis o de pago) [1038/nm0513-514](#)

**AUTORES / AUTHORS:** - Williams SC

[3]

**TÍTULO / TITLE:** - A prospective, multicenter validation study of a prognostic index composed of S-phase fraction, progesterone receptor status, and tumour

size predicts survival in node-negative breast cancer patients: NNBC, the node-negative breast cancer trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt186](#)

**AUTORES / AUTHORS:** - Klintman M; Nilsson F; Bendahl PO; Ferno M; Liljegren G; Emdin S; Malmstrom P

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Sciences, Division of Oncology, Lund University, Lund.

**RESUMEN / SUMMARY:** - **BACKGROUND:** In a retrospective study on node-negative breast cancer, a prognostic index consisting of a proliferation factor, S-phase fraction (SPF), progesterone receptor status (PR), and tumour size identified one-third of patients as high risk, with a sixfold increased risk of breast cancer death. This prospective multicenter cohort study was set up to validate the index. **PATIENTS AND METHODS:** In 576 T1-2N0 patients <60 years, prospective analyses of PR and SPF were carried out. High risk was defined as  $\geq 2$  of the following: size >20 mm, PR-negativity, and high SPF (in the absence of SPF, Bloom-Richardson grade 3). Median follow-up was 17.8 years. **RESULTS:** Thirty-one percent were high risk. In univariate analysis, the index was prognostic for breast cancer-specific survival after 5 years [hazard ratio (HR) = 4.7, 95% confidence interval (95% CI) 2.5-8.9], 10 years (HR = 2.2, 95% CI 1.5-3.3), and 15 years (HR = 1.7, 95% CI 1.2-2.5), and remained significant after adjustment for adjuvant medical treatment and age. In the 37% of patients with no risk factors, only one patient died of breast cancer the first 5 years. **CONCLUSIONS:** This prospective study validates a prognostic index consisting of a proliferation factor, PR-status, and tumour size. The index may be helpful for prognostic considerations and for selection of patients in need of adjuvant therapy.

[4]

**TÍTULO / TITLE:** - A randomised phase III intergroup trial comparing high-dose infusional 5-fluorouracil with or without folinic acid with standard bolus 5-fluorouracil/folinic acid in the adjuvant treatment of stage III colon cancer: The Pan-European Trial in Adjuvant Colon Cancer 2 study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 May;49(8):1868-75. doi: 10.1016/j.ejca.2013.01.030. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.01.030](#)

**AUTORES / AUTHORS:** - Kohne CH; Bedenne L; Carrato A; Bouche O; Popov I; Gaspa L; Valladares M; Rougier P; Gog C; Reichardt P; Wils J; Pignatti F; Biertz F

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University, Oldenburg, Germany. Electronic address: [onkologie@klinikum-oldenburg.de](mailto:onkologie@klinikum-oldenburg.de).

**RESUMEN / SUMMARY:** - PURPOSE: To investigate whether infusional high-dose 5-fluorouracil (HD-FU) provides a significant improvement in recurrence-free survival (RFS) and overall survival (OS) compared with a standard bolus 5-FU regimen (Mayo Clinic) in patients with curatively resectable stage III colon cancer. METHODS: Patients (n=1601) were randomised to receive either the Mayo Clinic regimen or one of the three HD-FU regimens; LV5FU2, the Arbeitsgemeinschaft Internistische Onkologie (AIO) or the Grupo Español para el Tratamiento Digestivos (TTD), the data from which were combined to provide the HD-FU arm for final analysis. RESULTS: Patients were evenly balanced for age, TMN, tumor grade and vascular and lymphatic invasion. Median follow-up was approximately 42 months, RFS (hazard ratio [HR]=0.997) and OS (HR=0.96) (primary end-point) were not statistically different between the two treatment arms. Infusional HD-FU was generally better tolerated than bolus 5-FU regimen. CONCLUSIONS: Infusional HD-FU does not improve RFS and OS in curatively resected stage III colon cancer patients compared to the Mayo Clinic regimen, but is less toxic.

[5]

**TÍTULO / TITLE:** - Specific Adverse Events Predict Survival Benefit in Patients Treated With Tamoxifen or Aromatase Inhibitors: An International Tamoxifen Exemestane Adjuvant Multinational Trial Analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.45.3068](https://doi.org/10.1200/JCO.2012.45.3068)

**AUTORES / AUTHORS:** - Fontein DB; Seynaeve C; Hadji P; Hille ET; van de Water W; Putter H; Kranenbarg EM; Hasenburg A; Paridaens RJ; Vannetzel JM; Markopoulos C; Hozumi Y; Bartlett JM; Jones SE; Rea DW; Nortier JW; van de Velde CJ

**INSTITUCIÓN / INSTITUTION:** - Duveken B.Y. Fontein, Elysee T.M. Hille, Willemien van de Water, Hein Putter, Elma Meershoek-Klein Kranenbarg, Johan W.R. Nortier, and Cornelis J.H. van de Velde, Leiden University Medical Center, Leiden; Caroline Seynaeve, Erasmus Medical Center-Daniel den Hoed, Rotterdam, the Netherlands; Peyman Hadji, Philipps University of Marburg, Marburg; Annette Hasenburg, University Hospital Freiburg, Freiburg, Germany; Robert J. Paridaens, University Hospital Gasthuisberg, Leuven, Belgium; Jean-Michel Vannetzel, Institut du Sein Henri Hartmann, Neuilly sur Seine, France; Christos Markopoulos, Athens University Medical School, Athens, Greece; Yasuo Hozumi, Jichi Medical University, Shimotsuko, Japan; John M.S. Bartlett, Edinburgh University, Edinburgh; Daniel Rea, University of Birmingham, Birmingham, United Kingdom; and Stephen E. Jones, US Oncology Research, the Woodlands, TX.

**RESUMEN / SUMMARY:** - PURPOSE Specific adverse events (AEs) associated with endocrine therapy and related to depletion or blocking of circulating estrogens may be related to treatment efficacy. We investigated the relationship between survival outcomes and specific AEs including vasomotor symptoms (VMSs), musculoskeletal adverse events (MSAEs), and vulvovaginal symptoms (VVSs) in postmenopausal patients with breast cancer participating in the international Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. PATIENTS AND METHODS Primary efficacy end points were disease-free survival (DFS), overall survival (OS), and distant metastases (DM). VMSs, MSAEs, and VVSs arising in the first year of endocrine treatment were considered. Patients who did not start or who discontinued their allocated therapy and/or had an event (recurrence/death) within 1 year after randomization were excluded. Landmark analyses and time-dependent multivariate Cox proportional hazards models assessed survival differences up to 5 years from the start of treatment. RESULTS: VMSs, 0.731 [95% CI, 0.618 to 0.866]; MSAEs, 0.826 [95% CI, 0.694 to 0.982]; VVSs, 0.769 [95% CI, 0.585 to 1.01]; multivariate HR for OS: VMSs, 0.583 [95% CI, 0.424 to 0.803]; MSAEs, 0.811 [95% CI, 0.654 to 1.005]; VVSs, 0.570 [95% CI, 0.391 to 0.831]) and fewer DM (VMSs, 0.813 [95% CI, 0.664 to 0.996]; MSAEs, 0.749 [95% CI, 0.601 to 0.934]; VVSs, 0.687 [95% CI, 0.436 to 1.085]) than patients not reporting these symptoms. Increasing numbers of specific AEs were also associated with better survival outcomes. Outcomes were unrelated to treatment allocation. CONCLUSION Certain specific AEs are associated with superior survival outcomes and may therefore be useful in predicting treatment responses in patients with breast cancer treated with endocrine therapy.

[6]

**TÍTULO / TITLE:** - G protein-coupled estrogen receptor is apoptotic and correlates with increased distant disease-free survival of estrogen receptor-positive breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Apr 1;19(7):1681-92. doi: 10.1158/1078-0432.CCR-12-2376.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-2376](#)

**AUTORES / AUTHORS:** - Broselid S; Cheng B; Sjöström M; Lovgren K; Klug-De Santiago HL; Belting M; Jirstrom K; Malmstrom P; Olde B; Bendahl PO; Hartman L; Ferno M; Leeb-Lundberg LM

**INSTITUCIÓN / INSTITUTION:** - Department of Experimental Medical Science, Lund University, Lund, Sweden.

**RESUMEN / SUMMARY:** - PURPOSE: G protein-coupled estrogen receptor 1 (GPER1), previously named GPR30, is a membrane receptor reported to mediate nongenomic estrogen responses. We investigated if GPER1

expression correlates with any clinicopathologic variables and distant disease-free survival (DDFS) in patients with breast cancer, if any prognostic impact of the receptor is dependent on estrogen receptor-alpha (ER-alpha) status, and if the receptor impacts apoptotic signaling in ER-positive breast cancer cells. EXPERIMENTAL DESIGN: GPER1 expression was analyzed by immunohistochemistry in breast tumors from 273 pre- and postmenopausal stage II patients, all treated with adjuvant tamoxifen for 2 years (cohort I) and from 208 premenopausal lymph node-negative patients, of which 87% were not subjected to any adjuvant systemic treatment (cohort II). GPER1-dependent proapoptotic signaling was analyzed in MCF7 cells with and without GPER1 knockdown, T47D cells, HEK293 cells (HEK), and HEK stably expressing GPER1 (HEK-R). RESULTS: GPER1 positively correlates with ER and progesterone receptor expression. Multivariate analysis showed that GPER1 is an independent prognostic marker of increased 10-year DDFS in the ER-positive subgroup. HEK-R has higher basal proapoptotic signaling compared with HEK including increased cytochrome C release, caspase-3 cleavage, PARP cleavage, and decreased cell viability. Treating HEK-R with the proteasome inhibitor epoxomicin, to decrease GPER1 degradation, further increases receptor-dependent proapoptotic signaling. Also, GPER1 knockdown decreases basal and agonist-stimulated proapoptotic receptor signaling in MCF7 cells. CONCLUSIONS: GPER1 is a prognostic indicator for increased DDFS in ER-positive breast cancer, which may be associated with constitutive GPER1-dependent proapoptotic signaling in ER-positive breast cancer cells.

[7]

**TÍTULO / TITLE:** - Consolidation treatment with Yttrium-90 ibritumomab tiuxetan after a new induction regimen in intermediate and high-risk follicular lymphoma patients according to the follicular lymphoma international prognostic index (FLIPI): A multicenter, prospective Phase II trial of Spanish Lymphoma Oncology Group.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.790544](#)

**AUTORES / AUTHORS:** - Provencio M; Cruz Mora MA; Gomez Codina J; Quero Blanco C; Llanos M; Garcia Arroyo FR; De la Cruz L; Guma Padro J; Delgado Perez JR; Sanchez A; Alvarez Cabellos R; Rueda A

**RESUMEN / SUMMARY:** - Abstract Relapse is the main cause of therapeutic failure in Follicular Lymphoma (FL). We set out to evaluate the role of consolidation with yttrium-90 ibritumomab tiuxetan in intermediate and high-risk FL patients after four cycles of CHOP-R and two CHOP cycles. 30 patients were included. The overall response rate after consolidation therapy was 93%. Of the 18 patients who presented partial remission after the induction treatment,

11 had complete remission after the consolidation treatment. The complete clinical response rate was 76.6%. The most important G 3 / 4 toxicity was hematological, with 46% thrombopenia and 56% neutropenia. With median follow-up of 26 months the means for progression-free survival or overall survival were not reached. Our data support consolidation treatment with yttrium-90 ibritumomab tiuxetan as an effective treatment, and it provides a long progression-free survival and overall survival in first line after response to induction treatment in intermediate and high-risk FL patients.

[8]

**TÍTULO / TITLE:** - A multivariate analysis of the relationship between response and survival among patients with higher-risk myelodysplastic syndromes treated within azacitidine or conventional care regimens in the randomized AZA-001 trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 May 28.

●●Enlace al texto completo (gratis o de pago)

[3324/haematol.2012.074831](#)

**AUTORES / AUTHORS:** - Gore SD; Fenaux P; Santini V; Bennett JM; Silverman LR; Seymour JF; Hellstrom-Lindberg E; Swern AS; Beach CL; List AF

**INSTITUCIÓN / INSTITUTION:** - USA;

**RESUMEN / SUMMARY:** - The phase III AZA-001 study established that azacitidine significantly improves overall survival compared with conventional care regimens (hazard ratio 0.58 [95% confidence interval 0.43-0.77],  $P < 0.001$ ). This analysis was conducted to investigate the relationship between treatment response and overall survival. AZA-001 data were analyzed in a multivariate Cox regression analysis with response as a time-varying covariate. Response categories were Overall Response, which was defined as complete remission, partial remission, or any hematologic improvement; and "Stable Disease," defined as no complete or partial remission, hematologic improvement, or progression; or Other (e.g., disease progression). Achieving an Overall Response with azacitidine reduced risk of death by 95% compared with achieving an Overall Response with the conventional care regimens (hazard ratio 0.05 [0.01-0.43],  $p = 0.006$ ). Sensitivity analyses indicated that significantly improved overall survival remained manifest for patients with a hematologic improvement who had never achieved complete or partial remission (hazard ratio 0.19 [0.08-0.46],  $p < 0.001$ ). Stable Disease in both azacitidine-treated and conventional care-treated patients was also associated with a significantly reduced risk of death (hazard ratio 0.09, [0.06&-0.15];  $p < 0.001$ ). These results demonstrate azacitidine benefit on overall survival compared with conventional care regimens in patients with higher-risk myelodysplastic syndromes who achieve hematologic response but never attain complete or partial remission, in addition to the survival advantage conferred by achievement of complete or

partial remission. This study was registered with [clinicaltrials.gov](http://clinicaltrials.gov) (NCT00071799).

[9]

**TÍTULO / TITLE:** - Multicenter Phase II Study of Neoadjuvant Lapatinib and Trastuzumab With Hormonal Therapy and Without Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 2-Overexpressing Breast Cancer: TBCRC 006.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 10;31(14):1726-31. doi: 10.1200/JCO.2012.44.8027. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.44.8027](http://1200/JCO.2012.44.8027)

**AUTORES / AUTHORS:** - Rimawi MF; Mayer IA; Forero A; Nanda R; Goetz MP; Rodriguez AA; Pavlick AC; Wang T; Hilsenbeck SG; Gutierrez C; Schiff R; Osborne CK; Chang JC

**INSTITUCIÓN / INSTITUTION:** - Baylor College of Medicine, One Baylor Plaza, Breast Center, BCM 660, Houston, TX 77030; [rimawi@bcm.edu](mailto:rimawi@bcm.edu).

**RESUMEN / SUMMARY:** - **PURPOSE** We previously reported the eradication of human epidermal growth factor receptor 2 (HER2)- amplified human xenografts in mice by inhibition of the HER2 pathway with lapatinib and trastuzumab to block all homo- and heterodimer signaling as well as by blockade of estrogen receptor (ER) when expressed. In this clinical trial, we sought to translate these findings to patients using targeted therapy without chemotherapy. **PATIENTS AND METHODS** Women with stages II to III HER2-positive breast cancers were eligible. They received trastuzumab once per week (4 mg/kg loading, then 2 mg/kg) and lapatinib 1000 mg once per day for 12 weeks. Women with ER-positive tumors also received letrozole (plus a luteinizing hormone-releasing hormone [LHRH] agonist if premenopausal). Pathologic response was assessed by ER status. Biopsies were obtained at baseline, weeks 2 and 8, and time of surgery. Results Sixty-six patients were enrolled, and 64 were eligible and evaluable for response. Median tumor size was 6 cm (range, 1.5 to 30 cm). Adverse events were mainly grades 1 to 2 (GI, 63%; skin, 46%). Grade 3 metabolic, GI, and liver (18%; 12 patients) and grade 4 liver toxicities (one patient) were also observed. Overall, in-breast pathologic complete response (pCR; ypT0-is) was 27% (ER positive, 21%; ER negative, 36%). The rate of low-volume residual disease (ypT1a-b) was 22% (ER positive, 33%; ER negative, 4%). **CONCLUSION** In patients with locally advanced HER2-positive breast cancer, our approach of targeted therapy only resulted in a high pCR rate without chemotherapy. Our data support the hypothesis that selected patients with HER2-positive tumors may not need chemotherapy, and more-complete blockade of HER receptors and ER is an effective strategy worthy of further study.

[10]

**TÍTULO / TITLE:** - Impact of PTEN Protein Expression on Benefit From Adjuvant Trastuzumab in Early-Stage Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the North Central Cancer Treatment Group N9831 Trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 6.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.42.2642](#)

**AUTORES / AUTHORS:** - Perez EA; Dueck AC; McCullough AE; Chen B; Geiger XJ; Jenkins RB; Lingle WL; Davidson NE; Martino S; Kaufman PA; Kutteh LA; Sledge GW; Harris LN; Gralow JR; Reinholz MM

**INSTITUCIÓN / INSTITUTION:** - Edith A. Perez and Xochiquetzal Geiger, Mayo Clinic, Jacksonville, FL; Amylou C. Dueck and Ann E. McCullough, Mayo Clinic, Scottsdale, AZ; Beiyun Chen, Robert B. Jenkins, Wilma L. Lingle, and Monica M. Reinholz, Mayo Clinic, Rochester, MN; Nancy E. Davidson, University of Pittsburgh Cancer Institute, Pittsburgh, PA; Silvana Martino, Angeles Clinic and Research Institute, Santa Monica, CA; Peter A. Kaufman, Dartmouth Hitchcock Medical Center, Lebanon, NH; Leila A. Kutteh, Oncology Associates of Cedar Rapids, Cedar Rapids, IA; George W. Sledge, Indiana University Medical Center Cancer Pavilion, Indianapolis, IN; Lyndsay N. Harris, Yale University, New Haven, CT; and Julie R. Gralow, Seattle Cancer Care Alliance, Seattle, WA.

**RESUMEN / SUMMARY:** - PURPOSE It has been suggested that PTEN, a negative regulator of PI3K/AKT signaling, is involved in tumor sensitivity to trastuzumab. We investigated the association between tumor PTEN protein expression and disease-free survival (DFS) of patients randomly assigned to receive chemotherapy alone (arm A) or chemotherapy with sequential (arm B) or concurrent trastuzumab (arm C) in the phase III early-stage human epidermal growth factor receptor 2 (HER2) -positive trial-North Central Cancer Treatment Group (NCCTG) N9831. PATIENTS AND METHOD The intensity and percentage of invasive cells with cytoplasmic PTEN staining were determined in tissue microarray sections containing three cores per block (n = 1,286) or in whole tissue sections (WS; n = 516) by using standard immunohistochemistry (138G6 monoclonal antibody). Tumors were considered positive for PTEN (PTEN-positive) if any core or WS had any invasive cells with  $\geq 1+$  staining. Median follow-up was 6.0 years. Results Of 1,802 patients included in this analysis (of 3,505 patients registered to N9831), 1,342 (74%) had PTEN-positive tumors. PTEN positivity was associated with hormone receptor negativity ( $\chi^2 P < .001$ ) and nodal positivity ( $\chi^2 P = .04$ ). PTEN did not have an impact on DFS within the various arms. Comparing DFS of arm C to arm A, patients with PTEN-positive and PTEN-negative tumors had hazard ratios (HRs) of 0.65 ( $P = .003$ ) and 0.47 ( $P = .005$ ), respectively (interaction  $P = .16$ ). For arm B versus arm A, patients with PTEN-positive and PTEN-negative

tumors had HRs of 0.70 (P = .009) and 0.85 (P = .44), respectively (interaction P = .47). CONCLUSION In contrast to selected preclinical and limited clinical studies suggesting a decrease in trastuzumab sensitivity in patients with PTEN-negative tumors, our data show benefit of adjuvant trastuzumab for patients with HER2-positive breast cancer, independent of tumor PTEN status.

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[11]

**TÍTULO / TITLE:** - A colorectal cancer classification system that associates cellular phenotype and responses to therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nat Med. 2013 May;19(5):619-25. doi: 10.1038/nm.3175. Epub 2013 Apr 14.

●●Enlace al texto completo (gratis o de pago) [1038/nm.3175](#)

**AUTORES / AUTHORS:** - Sadanandam A; Lyssiotis CA; Homicsko K; Collisson EA; Gibb WJ; Wullschleger S; Ostos LC; Lannon WA; Grotzinger C; Del Rio M; Lhermitte B; Olshen AB; Wiedenmann B; Cantley LC; Gray JW; Hanahan D

**INSTITUCIÓN / INSTITUTION:** - [1] Swiss Institute of Bioinformatics, Lausanne, Switzerland. [2] Swiss Institute for Experimental Cancer Research, Swiss Federal Institute of Technology Lausanne (EPFL), Lausanne, Switzerland.

**RESUMEN / SUMMARY:** - Colorectal cancer (CRC) is a major cause of cancer mortality. Whereas some patients respond well to therapy, others do not, and thus more precise, individualized treatment strategies are needed. To that end, we analyzed gene expression profiles from 1,290 CRC tumors using consensus-based unsupervised clustering. The resultant clusters were then associated with therapeutic response data to the epidermal growth factor receptor-targeted drug cetuximab in 80 patients. The results of these studies define six clinically relevant CRC subtypes. Each subtype shares similarities to distinct cell types within the normal colon crypt and shows differing degrees of 'stemness' and Wnt signaling. Subtype-specific gene signatures are proposed to identify these subtypes. Three subtypes have markedly better disease-free survival (DFS) after surgical resection, suggesting these patients might be spared from the adverse effects of chemotherapy when they have localized disease. One of these three subtypes, identified by filamin A expression, does not respond to cetuximab but may respond to cMET receptor tyrosine kinase inhibitors in the metastatic setting. Two other subtypes, with poor and intermediate DFS, associate with improved response to the chemotherapy regimen FOLFIRI in adjuvant or metastatic settings. Development of clinically deployable assays for these subtypes and of subtype-specific therapies may contribute to more effective management of this challenging disease.

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[12]

**TÍTULO / TITLE:** - Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - N Engl J Med. 2013 Apr 11;368(15):1408-16. doi: 10.1056/NEJMoa1214561.

●●Enlace al texto completo (gratis o de pago) [1056/NEJMoa1214561](#)

**AUTORES / AUTHORS:** - Dunleavy K; Pittaluga S; Maeda LS; Advani R; Chen CC; Hessler J; Steinberg SM; Grant C; Wright G; Varma G; Staudt LM; Jaffe ES; Wilson WH

**INSTITUCIÓN / INSTITUTION:** - Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Primary mediastinal B-cell lymphoma is a distinct subtype of diffuse large-B-cell lymphoma that is closely related to nodular sclerosing Hodgkin's lymphoma. Patients are usually young and present with large mediastinal masses. There is no standard treatment, but the inadequacy of immunochemotherapy alone has resulted in routine consolidation with mediastinal radiotherapy, which has potentially serious late effects. We aimed to develop a strategy that improves the rate of cure and obviates the need for radiotherapy. METHODS: We conducted a single-group, phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) and filgrastim without radiotherapy in 51 patients with untreated primary mediastinal B-cell lymphoma. We used results from a retrospective study of DA-EPOCH-R from another center to independently verify the outcomes. RESULTS: The patients had a median age of 30 years (range, 19 to 52) and a median tumor diameter of 11 cm; 59% were women. During a median of 5 years of follow-up, the event-free survival rate was 93%, and the overall survival rate was 97%. Among the 16 patients who were involved in the retrospective analysis at another center, over a median of 3 years of follow-up, the event-free survival rate was 100%, and no patients received radiotherapy. No late morbidity or cardiac toxic effects were found in any patients. After follow-up ranging from 10 months to 14 years, all but 2 of the 51 patients (4%) who received DA-EPOCH-R alone were in complete remission. The 2 remaining patients received radiotherapy and were disease-free at follow-up. CONCLUSIONS: Therapy with DA-EPOCH-R obviated the need for radiotherapy in patients with primary mediastinal B-cell lymphoma. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00001337.).

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[13]

**TÍTULO / TITLE:** - alphavbeta3 Integrin and Fibroblast growth factor receptor 1 (FGFR1): Prognostic factors in a phase I-II clinical trial associating continuous administration of Tipifarnib with radiotherapy for patients with newly diagnosed glioblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Apr 5. pii: S0959-8049(13)00172-X. doi: 10.1016/j.ejca.2013.02.033.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.02.033](#)

**AUTORES / AUTHORS:** - Ducassou A; Uro-Coste E; Verrelle P; Filleron T; Benouaich-Amiel A; Lubrano V; Sol JC; Delisle MB; Favre G; Ken S; Laprie A; De Porre P; Toulas C; Poublanc M; Cohen-Jonathan Moyal E

**INSTITUCIÓN / INSTITUTION:** - Institut Claudius Regaud, Departement de Radiotherapie, Toulouse F-31000, France.

**RESUMEN / SUMMARY:** - BACKGROUND: Based on our previous results showing the involvement of the farnesylated form of RhoB in glioblastoma radioresistance, we designed a phase II trial associating the farnesyltransferase inhibitor Tipifarnib with radiotherapy in patients with glioblastoma and studied the prognostic values of the proteins which we have previously shown control this pathway. PATIENTS AND METHODS: Patients were treated with 200mg Tipifarnib (recommended dose (RD)) given continuously during radiotherapy. Twenty-seven patients were included in the phase II whose primary end-point was time to progression (TTP). Overall survival (OS) and biomarker analysis were secondary end-points. Expressions of alphavbeta3, alphavbeta5 integrins, FAK, ILK, fibroblast growth factor 2 (FGF2) and fibroblast growth factor receptor 1 (FGFR1) were studied by immuno-histochemistry in the tumour of the nine patients treated at the RD during the previously performed phase I and on those of the phase II patients. We evaluated the correlation of the expressions of these proteins with the clinical outcome. RESULTS: For the phase II patients median TTP was 23.1weeks (95%CI=[15.4; 28.2]) while the median OS was 80.3weeks (95%CI=[57.8; 102.7]). In the pooled phase I and II population, median OS was 60.4w (95%CI=[47.3; 97.6]) while median TTP was 18.1w (95%CI=[16.9; 25.6]). FGFR1 over-expression (HR=4.65; 95%CI=[1.02; 21.21], p=0.047) was correlated with shorter TTP while FGFR1 (HR=4.1 (95% CI=[1.09-15.4]; p=0.036)) and alphavbeta3 (HR=10.38 (95%CI=[2.70; 39.87], p=0.001)) over-expressions were associated with reduced OS. CONCLUSION: Association of 200mg Tipifarnib with radiotherapy shows promising OS but no increase in TTP compared to historical data. FGFR1 and alphavbeta3 integrin are independent bad prognostic factors of OS and TTP.

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[14]

**TÍTULO / TITLE:** - High-dose imatinib versus high-dose imatinib in combination with intermediate-dose cytarabine in patients with first chronic phase myeloid leukemia: a randomized phase III trial of the Dutch-Belgian HOVON study group.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1730-4](http://1007/s00277-013-1730-4)

**AUTORES / AUTHORS:** - Thielen N; van der Holt B; Verhoef GE; Ammerlaan RA; Sonneveld P; Janssen JJ; Deenik W; Falkenburg JH; Kersten MJ; Sinnige HA; Schipperus M; Schattenberg A; van Marwijk Kooy R; Smit WM; Chu IW; Valk PJ; Ossenkoppele GJ; Cornelissen JJ

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, VU University Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands, [n.thielen@vumc.nl](mailto:n.thielen@vumc.nl).

**RESUMEN / SUMMARY:** - Despite the revolutionary change in the prognosis of chronic myeloid leukemia (CML) patients with the introduction of imatinib, patients with resistant disease still pose a considerable problem. In this multicenter, randomized phase III trial, we investigate whether the combination of high-dose imatinib and intermediate-dose cytarabine compared to high-dose imatinib alone, improves the rate of major molecular response (MMR) in newly diagnosed CML patients. This study was closed prematurely because of declining inclusion due to the introduction of second generation tyrosine kinase inhibitors and only one third of the initially required patients were accrued. One hundred nine patients aged 18-65 years were randomly assigned to either imatinib 800 mg (n = 55) or to imatinib 800 mg in combination with two successive cycles of cytarabine 200 mg/m<sup>2</sup> for 7 days (n = 54). After a median follow-up of 41 months, 67 % of patients were still on protocol treatment. The MMR rate at 12 months was 56 % in the imatinib arm and 48 % in the combination arm (p = 0.39). Progression-free survival was 96 % after 1 year and 89 % after 4 years. Four-year overall survival was 97 %. Adverse events grades 3 and 4 were more common in the combination arm. The addition of intermediate-dose of cytarabine to imatinib did not improve the MMR rate at 12 months. However, the underpowering of the study precludes any definitive conclusions. This trial is registered at [www.trialregister.nl](http://www.trialregister.nl) (NTR674).

[15]

**TÍTULO / TITLE:** - High-Dose Cytarabine Consolidation With or Without Additional Amsacrine and Mitoxantrone in Acute Myeloid Leukemia: Results of the Prospective Randomized AML2003 Trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.46.4743](http://1200/JCO.2012.46.4743)

**AUTORES / AUTHORS:** - Schaich M; Parmentier S; Kramer M; Illmer T; Stolzel F; Rollig C; Thiede C; Hanel M; Schafer-Eckart K; Aulitzky W; Einsele H; Ho AD; Serve H; Berdel WE; Mayer J; Schmitz N; Krause SW; Neubauer A; Baldus CD; Schetelig J; Bornhauser M; Ehninger G

**INSTITUCIÓN / INSTITUTION:** - Markus Schaich, Stefani Parmentier, Michael Kramer, Thomas Illmer, Friedrich Stolzel, Christoph Rollig, Christian Thiede,

Johannes Schetelig, Martin Bornhauser, and Gerhard Ehninger, Universitätsklinikum C.G. Carus, Dresden; Mathias Hanel, Klinikum Chemnitz, Chemnitz; Kerstin Schafer-Eckart, Klinikum Nord, Nurnberg; Walter Aulitzky, Robert-Bosch-Krankenhaus, Stuttgart; Hermann Einsele, Universitätsklinikum Wurzburg, Wurzburg; Anthony D. Ho, Universitätsklinikum Heidelberg, Heidelberg; Hubert Serve, Klinikum der J. W. Goethe Universität, Frankfurt; Wolfgang E. Berdel, Universitätsklinikum Munster, Munster; Norbert Schmitz, Asklepios Klinik St Georg, Hamburg; Stefan W. Krause, Universitätsklinikum Erlangen, Erlangen; Andreas Neubauer, Universitätsklinikum Giessen und Marburg, Marburg; Claudia D. Baldus, Charite-Universitätsmedizin Berlin, Berlin, Germany; and Jiri Mayer, University Hospital Brno and Masaryk University, Brno, Czech Republic.

**RESUMEN / SUMMARY:** - PURPOSE To assess the treatment outcome benefit of multiagent consolidation in young adults with acute myeloid leukemia (AML) in a prospective, randomized, multicenter trial. PATIENTS AND METHODS Between December 2003 and November 2009, 1,179 patients (median age, 48 years; range, 16 to 60 years) with untreated AML were randomly assigned at diagnosis to receive either standard high-dose cytarabine consolidation with three cycles of 18 g/m<sup>2</sup> (3x HD-AraC) or multiagent consolidation with two cycles of mitoxantrone (30 mg/m<sup>2</sup>) plus cytarabine (12 g/m<sup>2</sup>) and one cycle of amsacrine (500 mg/m<sup>2</sup>) plus cytarabine (10 g/m<sup>2</sup>; MAC/MAMAC/MAC). Allogeneic and autologous hematopoietic stem-cell transplantations were performed in a risk-adapted and priority-based manner. Results After double induction therapy using a 3 + 7 regimen including standard-dose cytarabine and daunorubicin, complete remission was achieved in 65% of patients. In the primary efficacy population of patients evaluable for consolidation outcomes, consolidation with either 3x HD-AraC or MAC/MAMAC/MAC did not result in any significant difference in 3-year overall (69% v 64%; P = .18) or disease-free survival (46% v 48%; P = .99) according to the intention-to-treat analysis. Furthermore, MAC/MAMAC/MAC led to additional GI and hepatic toxicity and a higher rate of infection and bleeding, resulting in significantly shorter 3-year overall survival in the per-protocol analysis compared with 3x HD-AraC (63% v 72%; P = .04). CONCLUSION In younger adults with AML, multiagent consolidation using mitoxantrone and amsacrine in combination with high-dose cytarabine does not improve treatment outcome and confers additional toxicity.

[16]

**TÍTULO / TITLE:** - Treatment-, Patient-, and Disease-Related Factors and the Emergence of Adverse Events with Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacotherapy. 2013 Apr 3. doi: 10.1002/phar.1266.

●●Enlace al texto completo (gratis o de pago) [1002/phar.1266](#)

**AUTORES / AUTHORS:** - Irvine E; Williams C

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, University of Kansas Hospital, Kansas City, Kansas.

**RESUMEN / SUMMARY:** - Four breakpoint cluster region (BCR)-ABL1 tyrosine kinase inhibitors (TKIs) are currently available for the treatment of chronic myeloid leukemia (CML): imatinib, nilotinib, dasatinib, and bosutinib. Choosing the most appropriate TKI requires clinicians to consider a host of patient-, disease-, and treatment-related factors, not the least of which include the safety profiles of the agents. This review discusses the potential impact of treatment-, patient-, and disease-related characteristics on the emergence of adverse events during TKI therapy, with a focus on the underlying mechanisms believed to be responsible for a number of important adverse events associated with these agents and what implications they may have for treatment choice, particularly in the setting of first-line treatment. A literature search of the PubMed database was conducted to identify articles that described the molecular mechanisms of BCR-ABL1-mediated leukemic transformation, the efficacy and safety of imatinib, nilotinib, dasatinib, and bosutinib in patients with CML, the kinase-binding spectrum of each TKI, and evidence suggesting a link between the TKI-binding profile and adverse events. The pattern of adverse events associated with each agent is important when selecting treatment with a TKI. Clinical studies suggest that imatinib, nilotinib, dasatinib, and bosutinib have differing safety profiles, which are in part attributable to the specificity and selectivity of each agent. Although much basic research must be conducted to further illuminate the mechanisms responsible for TKI-related adverse events, on- and off-target effects are believed to be at least partly responsible for cardiovascular toxicity, myelosuppression, fluid retention, gastrointestinal toxicity, and dermatologic toxicity. Increased understanding of the factors that affect TKI-associated adverse events and long-term safety data will enable a more informed approach to the selection of therapy best suited to the individual needs of patients with CML.

[17]

**TÍTULO / TITLE:** - Prognostic significance of the tumor-stroma ratio: validation study in node-negative premenopausal breast cancer patients from the EORTC perioperative chemotherapy (POP) trial (10854).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):371-9. doi: 10.1007/s10549-013-2571-5. Epub 2013 May 25.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2571-](http://dx.doi.org/10.1007/s10549-013-2571-5)

[5](#)

**AUTORES / AUTHORS:** - Dekker TJ; van de Velde CJ; van Pelt GW; Kroep JR; Julien JP; Smit VT; Tollenaar RA; Mesker WE

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Leiden University Medical Center, P.O. Box 9600 Albinusdreef, 2, 2300 RC, Leiden, The Netherlands, [t.j.a.dekker@lumc.nl](mailto:t.j.a.dekker@lumc.nl).

**RESUMEN / SUMMARY:** - The tumor-stroma ratio has previously been shown to be prognostic for patients with invasive breast cancer. We present a validation study to assess the prognostic significance in lymph node-negative, premenopausal patients from the perioperative chemotherapy trial (POP trial, 10854) conducted by the European Organization for Research and Treatment of Cancer. The POP trial assessed the efficacy of one course of perioperative chemotherapy (consisting of fluorouracil, doxorubicin, and cyclophosphamide). Hematoxylin and eosin (H&E) stained sections were retrieved from a subset of premenopausal, node-negative patients from this trial and were scored for the percentage of intra-tumoral stroma. The tumor-stroma ratio was associated with disease-free survival in univariate and multivariate analysis. Tumors with a high tumor-stroma ratio had an increased hazard of 1.853 for disease relapse (95 %CI 1.327-2.585, P < 0.001) independent of other parameters. Combining other parameters with the tumor-stroma ratio improved risk stratification. For triple-negative tumors, the tumor-stroma ratio was associated with an increased hazard for disease relapse, independent of other parameters (HR 2.711, 95 %CI 1.111-6.614, P = 0.028). The tumor-stroma ratio was also independently associated with locoregional recurrence even in breast cancer patients  $\leq 40$  years of age (HR 2.201, 95 %CI 1.038-4.669, P = 0.040). This study validates the prognostic value of the tumor-stroma ratio. This parameter can be easily assessed on HE slides and can be implemented next to pathological staging reports to determine patient prognosis.

[18]

**TÍTULO / TITLE:** - Role functioning before start of adjuvant treatment was an independent prognostic factor for survival and time to failure. A report from the Nordic adjuvant interferon trial for patients with high-risk melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Oncol. 2013 Apr 28.

●●Enlace al texto completo (gratis o de pago)

[3109/0284186X.2013.789140](#)

**AUTORES / AUTHORS:** - Brandberg Y; Johansson H; Aamdal S; Bastholt L; Hernberg M; Stierner U; von der Maase H; Hansson J

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden.

**RESUMEN / SUMMARY:** - Purpose. To investigate the role of health-related quality of life (HRQoL) at randomization as independent prognostic factors for survival and time to failure, and to explore associations between HRQoL and treatment effects. Material and methods. In the Nordic adjuvant interferon trial, a randomized trial evaluating if adjuvant therapy with intermediate-dose IFN had

the same beneficial effects on overall and disease-free survival in high-risk melanoma as high-dose IFN, 855 patients in Denmark, Finland, Norway, and Sweden were included. The EORTC QLQ-C30 questionnaire was used to assess HRQoL before randomization. Results. A total of 785 (92%) agreed to participate in the HRQoL-study and provided baseline HRQoL data. Prognostic variables included in the multivariate model were age, sex, performance status, tumor thickness, stage, and number of positive lymph nodes. Univariate analyses revealed an association between prolonged survival and age, stage/ number of metastatic lymph nodes and the HRQoL variable role functioning ( $p \leq 0.01$ ). After controlling for other prognostic factors, these variables remained independently statistically significant for survival. The univariate analyses of time to failure showed significant associations with the clinical variable stage/nodes and with the HRQoL variables physical functioning and role functioning. Adjusted multivariate analyses including the same clinical conditions as above showed statistically significant relationships between time to failure and global quality of life, physical functioning, role functioning, social functioning and fatigue ( $p \leq 0.01$ ). No interactions between HRQoL variables and treatment were found, with the exception for cognitive functioning. Conclusion. Role functioning was found to be an independent prognostic factor for time to failure and survival in patients with high-risk melanoma. Thus, also in this early stage of melanoma, HRQoL variables might be useful as important prognostic factors for time to failure and overall survival.

[19]

**TÍTULO / TITLE:** - Patients with chronic lymphocytic leukemia with high-risk genomic features have inferior outcome on successive Cancer and Leukemia Group B trials with alemtuzumab consolidation: subgroup analysis from CALGB 19901 and CALGB 10101.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 9.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.788179](#)

**AUTORES / AUTHORS:** - Jones JA; Ruppert AS; Zhao W; Lin TS; Rai K; Peterson B; Larson RA; Marcucci G; Heerema NA; Byrd JC

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology, The Ohio State University , Columbus, OH , USA.

**RESUMEN / SUMMARY:** - Alemtuzumab consolidation has been investigated to improve remission duration after fludarabine-based induction for chronic lymphocytic leukemia (CLL). The impact on genomic high-risk disease remains unknown. Cancer and Leukemia Group B (CALGB) 19901 and 10101 enrolled previously untreated patients to receive alemtuzumab consolidation after fludarabine-based induction. Immunoglobulin heavy chain gene (IGHV) mutation status and interphase cytogenetics were assessed retrospectively.

Treatment response with these alemtuzumab-containing regimens was similar, regardless of genomic risk, except for patients harboring del(17p), where few complete remissions were observed. Progression-free survival (PFS) was similar between IGVH groups, but overall survival (OS) was inferior in IGVH unmutated patients ( $p = 0.03$ ). Cytogenetic risk group was associated with PFS and OS ( $p = 0.01$  for both), with similarly short PFS in patients with del(17p) and del(11q) and particularly short OS in patients with del(17p). Cytogenetic risk group remained significantly associated with PFS and OS when controlling for other prognostic factors (PFS:  $p = 0.009$ ; OS:  $p = 0.02$ ), as did the negative association of IGVH unmutated disease with OS ( $p = 0.004$ ). Results were similar when restricting to patients who received at least one dose of alemtuzumab consolidation, demonstrating limited ability to overcome the poor outcome associated with high-risk genetic features (ClinicalTrials.gov identifiers: NCT00004857, NCT00098670).

[20]

**TÍTULO / TITLE:** - Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Immunity. 2013 Apr 18;38(4):729-41. doi: 10.1016/j.immuni.2013.03.003. Epub 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago)

[1016/j.immuni.2013.03.003](#)

**AUTORES / AUTHORS:** - Ma Y; Adjemian S; Mattarollo SR; Yamazaki T; Aymeric L; Yang H; Portela Catani JP; Hannani D; Duret H; Steegh K; Martins I; Schlemmer F; Michaud M; Kepp O; Sukkurwala AQ; Menger L; Vacchelli E; Droin N; Galluzzi L; Krzysiek R; Gordon S; Taylor PR; Van Endert P; Solary E; Smyth MJ; Zitvogel L; Kroemer G

**INSTITUCIÓN / INSTITUTION:** - Institut National de la Sante et de la Recherche Medicale, Villejuif, France.

**RESUMEN / SUMMARY:** - The therapeutic efficacy of anthracyclines relies on antitumor immune responses elicited by dying cancer cells. How chemotherapy-induced cell death leads to efficient antigen presentation to T cells, however, remains a conundrum. We found that intratumoral CD11c(+)CD11b(+)Ly6C(hi) cells, which displayed some characteristics of inflammatory dendritic cells and included granulomonocytic precursors, were crucial for anthracycline-induced anticancer immune responses. ATP released by dying cancer cells recruited myeloid cells into tumors and stimulated the local differentiation of CD11c(+)CD11b(+)Ly6C(hi) cells. Such cells efficiently engulfed tumor antigens in situ and presented them to T lymphocytes, thus vaccinating mice, upon adoptive transfer, against a challenge with cancer cells. Manipulations preventing tumor infiltration by CD11c(+)CD11b(+)Ly6C(hi) cells, such as the local overexpression of ectonucleotidases, the blockade of purinergic receptors,

or the neutralization of CD11b, abolished the immune system-dependent antitumor activity of anthracyclines. Our results identify a subset of tumor-infiltrating leukocytes as therapy-relevant antigen-presenting cells.

[21]

**TÍTULO / TITLE:** - Pooled Analysis of the Prognostic and Predictive Effects of KRAS Mutation Status and KRAS Mutation Subtype in Early-Stage Resected Non-Small-Cell Lung Cancer in Four Trials of Adjuvant Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.48.1390](https://doi.org/10.1200/JCO.2012.48.1390)

**AUTORES / AUTHORS:** - Shepherd FA; Domerg C; Hainaut P; Janne PA; Pignon JP; Graziano S; Douillard JY; Brambilla E; Le Chevalier T; Seymour L; Bourredjem A; Le Teuff G; Pirker R; Filipits M; Rosell R; Kratzke R; Bandarchi B; Ma X; Capelletti M; Soria JC; Tsao MS

**INSTITUCIÓN / INSTITUTION:** - Frances A. Shepherd, Bizhan Bandarchi, and Ming-Sound Tsao, University Health Network, Princess Margaret Hospital, and the University of Toronto, Toronto; Lesley Seymour, National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Ontario, Canada; Caroline Domerg, Jean-Pierre Pignon, Thierry Le Chevalier, Abderrahmane Bourredjem, Gwenael Le Teuff, and Jean-Charles Soria, Institut Gustave-Roussy and University Paris XI, Paris; Pierre Hainaut and Xiaoli Ma, International Agency for Research on Cancer, Lyon; Jean-Yves Douillard, Institut de Cancerologie de l'Ouest, St. Herblain; Elizabeth Brambilla, Inserm U823, Institut Albert Bonniot, Albert Michallon University Joseph Fourier, Grenoble, France; Pasi A. Janne and Marzia Capelletti, Dana Farber Cancer Institute, Boston, MA; Stephen Graziano, State University of New York Upstate Medical University, Syracuse, NY; Robert Pirker and Martin Filipits, Medical University of Vienna, Vienna, Austria; Rafael Rosell, Catalan Institute Oncology, Hospital Germans Trias i Pujol, Badalona, España; and Robert Kratzke, University of Minnesota Medical School, Minneapolis, MN.

**RESUMEN / SUMMARY:** - PURPOSE We undertook this analysis of KRAS mutation in four trials of adjuvant chemotherapy (ACT) versus observation (OBS) to clarify the prognostic/predictive roles of KRAS in non-small-cell lung cancer (NSCLC). METHODS KRAS mutation was determined in blinded fashion. Exploratory analyses were performed to characterize relationships between mutation status and subtype and survival outcomes using a multivariable Cox model. RESULTS: G12A or G12R (HR = 0.66; P = .48), G12C or G12V (HR = 0.94; P = .77) and G12D or G12S (HR = 1.39; P = .48; comparison of four HRs, including WT, interaction P = .76). OBS patients with KRAS-mutated tumors were more likely to develop second primary cancers (HR = 2.76, 95% CI, 1.34 to 5.70; P = .005) but not ACT patients (HR = 0.66; 95% CI, 0.25 to 1.75; P = .40; interaction, P = .02). CONCLUSION KRAS mutation status is not

significantly prognostic. The potential interaction in patients with codon-13 mutations requires validation. At this time, KRAS status cannot be recommended to select patients with NSCLC for ACT.

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[22]

**TÍTULO / TITLE:** - Prognostic microRNA/mRNA signature from the integrated analysis of patients with invasive breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proc Natl Acad Sci U S A. 2013 Apr 30;110(18):7413-7. doi: 10.1073/pnas.1304977110. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago) [1073/pnas.1304977110](http://1073/pnas.1304977110)

**AUTORES / AUTHORS:** - Volinia S; Croce CM

**INSTITUCIÓN / INSTITUTION:** - Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, 44121 Ferrara, Italy.

**RESUMEN / SUMMARY:** - The optimal management of breast cancer (BC) presents challenges due to the heterogeneous molecular classification of the disease. We performed survival analysis on a cohort of 466 patients with primary invasive ductal carcinoma (IDC), the most frequent type of BC, by integrating mRNA, microRNA (miRNA), and DNA methylation next-generation sequencing data from The Cancer Genome Atlas (TCGA). Expression data from eight other BC cohorts were used for validation. The prognostic value of the resulting miRNA/mRNA signature was compared with that of other prognostic BC signatures. Thirty mRNAs and seven miRNAs were associated with overall survival across different clinical and molecular subclasses of a 466-patient IDC cohort from TCGA. The prognostic RNAs included PIK3CA, one of the two most frequently mutated genes in IDC, and miRNAs such as hsa-miR-328, hsa-miR-484, and hsa-miR-874. The area under the curve of the receiver-operator characteristic for the IDC risk predictor in the TCGA cohort was 0.74 at 60 mo of overall survival ( $P < 0.001$ ). Most relevant for clinical application, the integrated signature had the highest prognostic value in early stage I and II tumors (receiver-operator characteristic area under the curve = 0.77,  $P$  value  $< 0.001$ ). The genes in the RNA risk predictor had an independent prognostic value compared with the clinical covariates, as shown by multivariate analysis. The integrated RNA signature was successfully validated on eight BC cohorts, comprising a total of 2,399 patients, and it had superior performance for risk stratification with respect to other RNA predictors, including the mRNAs used in MammaPrint and Oncotype DX assays.

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[23]

**TÍTULO / TITLE:** - Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade and Hormonal Therapy for the Treatment of Primary HER2-Positive Breast Cancer: One More Step Toward Chemotherapy-Free Therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 10;31(14):1703-6. doi: 10.1200/JCO.2012.48.4998. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.48.4998](#)

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[24]

**TÍTULO / TITLE:** - Randomized Phase II Study of Ixabepilone or Paclitaxel Plus Carboplatin in Patients With Non-Small-Cell Lung Cancer Prospectively Stratified by Beta-3 Tubulin Status.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Jun 1;31(16):1990-6. doi: 10.1200/JCO.2012.45.3282. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.45.3282](#)

**AUTORES / AUTHORS:** - Edelman MJ; Schneider CP; Tsai CM; Kim HT; Quoix E; Luft AV; Kaleta R; Mukhopadhyay P; Trifan OC; Whitaker L; Reck M

**INSTITUCIÓN / INSTITUTION:** - University of Maryland Greenebaum Cancer Center, Division of Hematology/Oncology, 22 South Green St, Baltimore, MD 21201-1595; [medelman@umm.edu](mailto:medelman@umm.edu).

**RESUMEN / SUMMARY:** - PURPOSE Retrospective studies have reported that tumor expression of the beta-3 tubulin (beta3T) isoform is an unfavorable prognostic factor in non-small-cell lung cancer (NSCLC) treated with tubulin-inhibiting chemotherapy. Ixabepilone is a tubulin-inhibiting agent with low susceptibility to multiple resistance mechanisms including beta3T isoform expression in several tumor models. This randomized phase II study evaluated ixabepilone-based chemotherapy in stage IIIb/IV NSCLC, compared with paclitaxel-based chemotherapy. Tumor specimens were prospectively evaluated for beta3T expression. PATIENTS AND METHODS Patients were stratified by beta3T status (positive v negative) and randomly assigned at a ratio of 1:1 to receive ixabepilone (32 mg/m<sup>2</sup>) and carboplatin (area under concentration-time curve [AUC], 6) or paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC, 6) for up to six cycles. The primary end point was progression-free survival (PFS) in the beta3T-positive subgroup. Results Ninety-five patients (beta3T positive, 52; beta3T negative, 43) received ixabepilone plus carboplatin; 96 patients (beta3T positive, 49; beta3T negative, 47) received paclitaxel plus carboplatin. No significant differences in median PFS were observed between arms for either subgroup (beta3T positive, 4.3 months in both arms; beta3T negative, 5.8 v 5.3 months). Ixabepilone did not significantly improve overall survival (OS) for the beta3T-positive subset or the overall population. Adverse events were similar between the two arms and comparable with those in previous studies. CONCLUSION There was no predictive value of

beta3T in differentiating clinical activity of ixabepilone- or paclitaxel-containing regimens. Ixabepilone did not improve PFS or OS in patients with beta3T-positive tumors. beta3T-positive patients had worse PFS relative to beta3T-negative patients, regardless of treatment; hence, beta3T expression seems to be a negative prognostic factor, but not a predictive factor, in advanced NSCLC treated with either ixabepilone or paclitaxel platinum-based doublets.

[25]

**TÍTULO / TITLE:** - Mammographic Density Reduction Is a Prognostic Marker of Response to Adjuvant Tamoxifen Therapy in Postmenopausal Patients With Breast Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.44.5015](#)

**AUTORES / AUTHORS:** - Li J; Humphreys K; Eriksson L; Edgren G; Czene K; Hall P

**INSTITUCIÓN / INSTITUTION:** - Jingmei Li, Genome Institute of Singapore, Singapore; Keith Humphreys, Louise Eriksson, Gustaf Edgren, Kamila Czene, and Per Hall, Karolinska Institutet, Stockholm, Sweden; and Gustaf Edgren, Harvard School of Public Health, Harvard University, Boston, MA.

**RESUMEN / SUMMARY:** - PURPOSE Tamoxifen treatment is associated with a reduction in mammographic density and an improved survival. However, the extent to which change in mammographic density during adjuvant tamoxifen therapy can be used to measure response to treatment is unknown. PATIENTS AND METHODS Overall, 974 postmenopausal patients with breast cancer who had both a baseline and a follow-up mammogram were eligible for analysis. On the basis of treatment information abstracted from medical records, 474 patients received tamoxifen treatment and 500 did not. Mammographic density was measured by using an automated thresholding method and expressed as absolute dense area. Change in mammographic density was calculated as percentage change from baseline. Survival analysis was performed by using delayed-entry Cox proportional hazards regression models, with death as a result of breast cancer as the end point. Analyses were adjusted for a range of patient and tumor characteristics. RESULTS During a 15-year follow-up, 121 patients (12.4%) died from breast cancer. Women treated with tamoxifen who experienced a relative density reduction of more than 20% between baseline and first follow-up mammogram had a reduced risk of death as a result of breast cancer of 50% (hazard ratio, 0.50; 95% CI, 0.27 to 0.93) compared with women with stable mammographic density. In the no-tamoxifen group, there was no statistically significant association between mammographic density change and survival. The survival advantage was not observed when absolute dense areas at baseline or follow-up were evaluated separately. CONCLUSION A decrease in mammographic density after breast cancer

diagnosis appears to serve as a prognostic marker for improved long-term survival in patients receiving adjuvant tamoxifen, and these data should be externally validated.

[26]

**TÍTULO / TITLE:** - Expression of both Estrogen Receptor-beta 1 (ER-beta1) and its co-regulator Steroid Receptor RNA Activator Protein (SRAP) are predictive for benefit from tamoxifen therapy in patients with Estrogen Receptor-alpha (ER-alpha)-Negative Early Breast Cancer (EBC).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt132](#)

**AUTORES / AUTHORS:** - Yan Y; Li X; Blanchard A; Bramwell VH; Pritchard KI; Tu D; Shepherd L; Myal Y; Penner C; Watson PH; Leygue E; Murphy LC

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Medical Genetics, Manitoba Institute of Cell Biology, CancerCare Manitoba, University of Manitoba, Winnipeg.

**RESUMEN / SUMMARY:** - BACKGROUND: Roles of Estrogen Receptor-beta 1 (ER-beta1) and its co-regulator Steroid Receptor RNA Activator Protein (SRAP) in breast cancer remain unclear. Previously, ER-beta1 and SRAP expression were found positively correlated in breast cancer and, therefore, expression of these two molecules could characterize cancers with a distinct clinical outcome. PATIENTS AND METHODS: ER-beta1 and SRAP expression was determined by immunohistochemistry (IHC) in tissue microarrays from a randomized, placebo-controlled trial (NCIC-CTG-MA12), designed to determine the benefit of tamoxifen following chemotherapy in premenopausal early breast cancer (EBC). Expression was dichotomized into low and high using median IHC scores. Relationships with survival used Cox modeling. RESULTS: In the whole cohort, ER-beta1 and SRAP were not prognostic. However, high ER-beta1 and SRAP significantly predicted tamoxifen responsiveness [overall survival, interaction test, P = 0.03; relapse-free survival (RFS), interaction test, P = 0.01]. Stratification by ER-alpha-status found predictive benefit only in ER-alpha-negative cases. The difference in RFS between tamoxifen and placebo was greater in patients whose tumors expressed both high SRAP and ER-beta1 [hazard ratio = 0.07; 95% confidence interval (CI) 0.01-0.41; P = 0.003] versus those with low SRAP or ER-beta1 (interaction test, P = 0.02). The interaction test was not significant in ER-alpha-positive cohorts. CONCLUSIONS: This study provides evidence that both ER-beta1 and SRAP could be predictive biomarkers of tamoxifen benefit in ER-alpha-negative premenopausal EBC.

[27]

**TÍTULO / TITLE:** - A UGT1A1\*28 and \*6 genotype-directed phase I dose-escalation trial of irinotecan with fixed-dose capecitabine in Korean patients with metastatic colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Jun;71(6):1609-17. doi: 10.1007/s00280-013-2161-6. Epub 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2161-](#)

[6](#)

**AUTORES / AUTHORS:** - Kim KP; Kim HS; Sym SJ; Bae KS; Hong YS; Chang HM; Lee JL; Kang YK; Lee JS; Shin JG; Kim TW

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology, Department of Medicine, Asan Medical Center, University of Ulsan College of Medicine, 86 Asanbyeongwon-gil, Songpa-ku, Seoul, 138-736, Korea.

**RESUMEN / SUMMARY:** - PURPOSE: UGT1A1 genotypes are important when considering treatment with irinotecan-containing regimens. In this study, we determined the dose, efficacy, and tolerability of irinotecan according to UGT1A1 genotypes when combined with capecitabine in patients with metastatic colorectal cancer. METHODS: Patients with histologically confirmed metastatic adenocarcinoma of the colon or rectum were enrolled into a UGT1A1 genotype-directed dose-escalation trial of irinotecan plus fixed-dose capecitabine (2,000 mg/m<sup>2</sup>/day). The starting dose of irinotecan was different for each genotype group and ranged from 200 to 280 mg/m<sup>2</sup>. Pharmacokinetic concentrations of irinotecan and metabolites were determined by LC/MS/MS. RESULTS: Fifty patients were genotyped for UGT1A1 \*28 and \*6, and grouped according to the numbers of defective alleles (DA): 0, 1, and 2. Plasma concentrations of irinotecan, SN-38, and SN-38G were measured. The maximum tolerated dose of irinotecan was 350 mg/m<sup>2</sup> for the 0 and 1 DA groups, and 200 mg/m<sup>2</sup> for the 2 DA group. For the 0, 1, and 2 DA groups, mean AUC<sub>last</sub> ratios of SN-38G to SN-38 were 7.72, 5.71, and 2.72 (P = 0.0023) and relative dose intensities at recommended dose were 85, 83, and 97 %. CONCLUSION: Irinotecan dosing based on UGT1A1\*28 and \*6 is feasible, and higher doses of irinotecan can be safely administered in patients with 0 or 1 DA, compared to those with 2 DA.

[28]

**TÍTULO / TITLE:** - Phase II study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-01-480228](#)

**AUTORES / AUTHORS:** - Ravandi F; Alattar ML; Grunwald MR; Rudek MA; Rajkhowa T; Richie MA; Pierce S; Daver N; Garcia-Manero G; Faderl S; Nazha

A; Konopleva M; Borthakur G; Burger J; Kadia T; Deltasala S; Andreeff M; Cortes J; Kantarjian H; Levis M

**INSTITUCIÓN / INSTITUTION:** - Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, United States;

**RESUMEN / SUMMARY:** - We examined the efficacy of combining sorafenib and 5-azacytidine (AZA) in patients with AML and the FLT3-ITD mutation. Patients received AZA 75 mg/m<sup>2</sup> IV daily for 7 days and sorafenib 400 mg PO twice daily continuously; cycles were repeated at approximately one month intervals. Forty-three AML patients with a median age of 64 years (range, 24-87) were enrolled; 37 were evaluable for response. The FLT-3-ITD mutation was detected in 40 (93%) patients with a median allelic ratio of 0.28 (range, 0 - 0.93). They had received a median of 2 prior treatment regimens (range, 0-7); 9 had failed prior therapy with a FLT3 kinase inhibitor. The response rate was 46%, including 10 (27%) CRi, 6 (16%) CR, and 1 (3%) PR. The median time to achieve CR/CRi was 2 cycles (Range, 1 - 4), and the median duration of CR/CRi was 2.3 months (Range, 1 - 14.3 months). 64% of patients achieved adequate (defined as >85%) FLT3 inhibition during their first cycle of therapy. The degree of FLT3 inhibition correlated with plasma sorafenib concentrations. FL levels did not rise to levels seen in prior studies of patients receiving cytotoxic chemotherapy. The combination of AZA and sorafenib is effective for patients with relapsed AML and the FLT-3-ITD mutation. (The study was registered on ClinicalTrials.gov as NCT01254890.)

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[29]

**TÍTULO / TITLE:** - CD44/cellular prion protein interact in multidrug resistant breast cancer cells and correlate with responses to neoadjuvant chemotherapy in breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 May 16. doi: 10.1002/mc.22021.

●●Enlace al texto completo (gratis o de pago) [1002/mc.22021](#)

**AUTORES / AUTHORS:** - Cheng Y; Tao L; Xu J; Li Q; Yu J; Jin Y; Chen Q; Xu Z; Zou Q; Liu X

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, School of Basic Medical Sciences, Fudan University, Shanghai, China.

**RESUMEN / SUMMARY:** - Multidrug resistance (MDR) is one of the most important factors leading to chemotherapeutic failure in patients with breast cancer. The invasive/metastatic ability of MDR cells is strengthened compared with their parental cells. However, the mechanisms underlying MDR have not been fully elucidated. We found that CD44 and the cellular prion protein (PrPc) were both overexpressed in MDR cells (MCF7/Adr and H69AR). Subsequently, we chose the human breast cancer cell line MCF7/Adr, which is resistant to adriamycin, for further research. We discovered that PrPc physically and functionally interacted with CD44. The knockdown of CD44 or PrPc by siRNA in MCF7/Adr

cells inhibited cell migration, invasion and proliferation in vitro. However, when the MCF7/Adr cells transfected with CD44 siRNA were incubated with 10 times the peak plasma concentration (PPC) of taxol, their invasive ability was again enhanced. In the breast-carcinoma tissue samples, a significant correlation between the CD44 expression and the PrPc expression was observed in the postneoadjuvant-chemotherapy (NAC) cases. Moreover, in Group 2, which was unresponsive to NAC, the CD44 and PrPc expression levels were significantly increased in the post-NAC cases compared with the pre-NAC cases using the paired-samples t-test. These data indicate that the CD44/PrPc interaction enhances the malignancy of breast cancer cells and affects the responses to neoadjuvant chemotherapy in breast cancer patients. Therefore, blocking the CD44/PrPc interaction may improve outcomes in chemorefractory breast cancer patients. © 2013 Wiley Periodicals, Inc.

[30]

**TÍTULO / TITLE:** - Polymorphisms in the XRCC1 gene modify survival of bladder cancer patients treated with chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Mar 30. doi: 10.1002/ijc.28186.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28186](http://1002/ijc.28186)

**AUTORES / AUTHORS:** - Sacerdote C; Guarrera S; Ricceri F; Pardini B; Polidoro S; Allione A; Critelli R; Russo A; Andrew AS; Ye Y; Wu X; Kiemeny LA; Bosio A; Casetta G; Cucchiarale G; Destefanis P; Gontero P; Rolle L; Zitella A; Fontana D; Vineis P; Matullo G

**INSTITUCIÓN / INSTITUTION:** - HuGeF Human Genetics Foundation, Torino, Italy; Unit of Cancer Epidemiology, University of Turin and Centre for Cancer Epidemiology and Prevention (CPO Piemonte), Torino, Italy.

**RESUMEN / SUMMARY:** - Survival of bladder cancer patients depends on several factors including disease stage and grade at diagnosis, age, health status of the patient and the applied treatment. Several studies investigated the role of DNA repair genetic variants in cancer susceptibility, but only few studies investigated their role in survival and response to chemotherapy for bladder cancer. We genotyped 28 single nucleotide polymorphisms (SNP) in DNA repair genes in 456 bladder cancer patients, reconstructed haplotypes and calculated a score for combinations of the SNPs. We estimated Hazard Ratios (adjHR) for time to death. Among patients treated with chemotherapy, variant alleles of five SNPs in the XRCC1 gene conferred better survival (rs915927 adjHR 0.55 (95%CI 0.32-0.94); rs76507 adjHR 0.48 (95%CI 0.27-0.84); rs2854501 adjHR 0.25 (95%CI 0.12-0.52); rs2854509 adjHR 0.21 (95%CI 0.09-0.46); rs3213255 adjHR 0.46 (95%CI 0.26-0.80)). In this group of patients, an increasing number of variant alleles in a XRCC1 gene score were associated with a better survival (26% decrease of risk of death for each additional variant allele in XRCC1). By functional analyses we demonstrated that the previous

XRCC1 SNPs confer lower DNA repair capacity. This may support the hypothesis that survival in these patients may be modulated by the different DNA repair capacity determined by genetic variants. Chemotherapy treated cancer patients bearing an increasing number of “risky” alleles in XRCC1 gene had a better survival, suggesting that a proficient DNA repair may result in resistance to therapy and shorter survival. This finding may have clinical implications for the choice of therapy.

[31]

**TÍTULO / TITLE:** - Primary Granulocyte Colony-Stimulating Factor Prophylaxis During the First Two Cycles Only or Throughout All Chemotherapy Cycles in Patients With Breast Cancer at Risk for Febrile Neutropenia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.44.6229](https://doi.org/10.1200/JCO.2012.44.6229)

**AUTORES / AUTHORS:** - Aarts MJ; Peters FP; Mandigers CM; Dercksen MW; Stouthard JM; Nortier HJ; van Laarhoven HW; van Warmerdam LJ; van de Wouw AJ; Jacobs EM; Mattijssen V; van der Rijt CC; Smilde TJ; van der Velden AW; Temizkan M; Batman E; Muller EW; van Gastel SM; Borm GF; Tjan-Heijnen VC

**INSTITUCIÓN / INSTITUTION:** - Maureen J. Aarts and Vivianne C.G. Tjan-Heijnen, Maastricht University Medical Center, Maastricht; Frank P. Peters, Orbis Medical Center, Sittard-Geleen; Caroline M. Mandigers, Canisius Wilhelmina Hospital; Hanneke W. van Laarhoven and George F. Borm, Radboud University Nijmegen Medical Center; Saskia M. van Gastel; Comprehensive Cancer Centre East; George F. Borm, Nijmegen I, Nijmegen; M. Wouter Dercksen, Maxima Medical Center, Veldhoven; Laurence J. van Warmerdam, Catharina Hospital, Eindhoven; Jacqueline M. Stouthard, Maasstad Medical Center; Carin C. van der Rijt, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam; Hans J. Nortier, Leiden University Medical Center; Erdogan Batman, Diaconessenhuis Leiden, Leiden; Agnes J. van de Wouw, VieCuri Medical Center, Venlo; Esther M. Jacobs, Elkerliek Hospital, Helmond; Vera Mattijssen, Rijnstate Hospital, Arnhem; Tineke J. Smilde, Jeroen Bosch Hospital, 's-Hertogenbosch; Annette W. van der Velden, Martini Hospital, Groningen; Mehmet Temizkan, Hospital St Jansdal, Harderwijk; and Erik W. Muller, Slingeland Hospital, Doetinchem, the Netherlands.

**RESUMEN / SUMMARY:** - PURPOSE Early breast cancer is commonly treated with anthracyclines and taxanes. However, combining these drugs increases the risk of myelotoxicity and may require granulocyte colony-stimulating factor (G-CSF) support. The highest incidence of febrile neutropenia (FN) and largest benefit of G-CSF during the first cycles of chemotherapy lead to questions about the effectiveness of continued use of G-CSF throughout later cycles of chemotherapy. PATIENTS AND METHODS In a multicenter study, patients with

breast cancer who were considered fit enough to receive 3-weekly polychemotherapy, but also had > 20% risk for FN, were randomly assigned to primary G-CSF prophylaxis during the first two chemotherapy cycles only (experimental arm) or to primary G-CSF prophylaxis throughout all chemotherapy cycles (standard arm). The noninferiority hypothesis was that the incidence of FN would be maximally 7.5% higher in the experimental compared with the standard arm. Results After inclusion of 167 eligible patients, the independent data monitoring committee advised premature study closure. Of 84 patients randomly assigned to G-CSF throughout all chemotherapy cycles, eight (10%) experienced an episode of FN. In contrast, of 83 patients randomly assigned to G-CSF during the first two cycles only, 30 (36%) had an FN episode (95% CI, 0.13 to 0.54), with a peak incidence of 24% in the third cycle (ie, first cycle without G-CSF prophylaxis). CONCLUSION In patients with early breast cancer at high risk for FN, continued use of primary G-CSF prophylaxis during all chemotherapy cycles is of clinical relevance and thus cannot be abandoned.

[32]

**TÍTULO / TITLE:** - Receipt of maintenance therapy is most predictive of survival in older acute lymphoblastic leukemia patients treated with intensive induction chemotherapy regimens.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Hematol. 2013 May 2. doi: 10.1002/ajh.23468.

●●Enlace al texto completo (gratis o de pago) [1002/ajh.23468](#)

**AUTORES / AUTHORS:** - Landsburg DJ; Stadtmauer E; Loren A; Goldstein S; Frey N; Nasta SD; Porter DL; Tsai DE; Perl AE; Hexner EO; Luger S

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology/Oncology, Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

**RESUMEN / SUMMARY:** - While the prognosis for older adults diagnosed with acute lymphoblastic leukemia (ALL) is frequently poor, long-term survival can be achieved in patients treated with curative intent. We reviewed the outcomes of 37 patients age  $\geq 60$  treated at our institution with either DVP- or hyperCVAD-based chemotherapy regimens from 2003-2011. In this patient population, a complete response rate of 92%, relapse rate of 56% and median overall survival of 18.1 months was experienced. Univariate analysis revealed that receipt of maintenance therapy vs. no maintenance therapy was associated with a statistically-significant impact on overall survival ( $p = 0.001$ , HR 0.15 for death), while disease-related characteristics including high-risk white blood cell count at diagnosis and Philadelphia chromosome status as well as treatment-related factors including chemotherapy regimen or completion of intensive therapy were not. Many patients were unable to initiate or remain on maintenance therapy due to toxicities including infections and cytopenias. Our

analysis reveals the benefit of prolonged therapy in the treatment of older adults with ALL as well as the high incidence of treatment-related toxicity experienced by these patients. Am. J. Hematol., 2013. © 2013 Wiley Periodicals, Inc.

[33]

**TÍTULO / TITLE:** - The retinoblastoma protein induces apoptosis directly at the mitochondria.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genes Dev. 2013 May 1;27(9):1003-15. doi: 10.1101/gad.211326.112. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1101/gad.211326.112](#)

**AUTORES / AUTHORS:** - Hilgendorf KI; Leshchiner ES; Nedelcu S; Maynard MA; Calo E; Ianari A; Walensky LD; Lees JA

**INSTITUCIÓN / INSTITUTION:** - David H. Koch Institute for Integrative Cancer Research at MIT, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA;

**RESUMEN / SUMMARY:** - The retinoblastoma protein gene RB-1 is mutated in one-third of human tumors. Its protein product, pRB (retinoblastoma protein), functions as a transcriptional coregulator in many fundamental cellular processes. Here, we report a nonnuclear role for pRB in apoptosis induction via pRB's direct participation in mitochondrial apoptosis. We uncovered this activity by finding that pRB potentiated TNFalpha-induced apoptosis even when translation was blocked. This proapoptotic function was highly BAX-dependent, suggesting a role in mitochondrial apoptosis, and accordingly, a fraction of endogenous pRB constitutively associated with mitochondria. Remarkably, we found that recombinant pRB was sufficient to trigger the BAX-dependent permeabilization of mitochondria or liposomes in vitro. Moreover, pRB interacted with BAX in vivo and could directly bind and conformationally activate BAX in vitro. Finally, by targeting pRB specifically to mitochondria, we generated a mutant that lacked pRB's classic nuclear roles. This mito-tagged pRB retained the ability to promote apoptosis in response to TNFalpha and also additional apoptotic stimuli. Most importantly, induced expression of mito-tagged pRB in Rb(-/-);p53(-/-) tumors was sufficient to block further tumor development. Together, these data establish a nontranscriptional role for pRB in direct activation of BAX and mitochondrial apoptosis in response to diverse stimuli, which is profoundly tumor-suppressive.

[34]

**TÍTULO / TITLE:** - Residual Lymph Node Disease After Neoadjuvant Chemotherapy Predicts an Increased Risk of Lymphedema in Node-Positive Breast Cancer Patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1245/s10434-012-2828-](https://doi.org/10.1245/s10434-012-2828-y)

[y](#)

**AUTORES / AUTHORS:** - Specht MC; Miller CL; Skolny MN; Jammallo LS; O'Toole J; Horick N; Isakoff SJ; Smith BL; Taghian AG

**INSTITUCIÓN / INSTITUTION:** - Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Axillary lymph node dissection (ALND) is recommended for patients with clinically node-positive breast cancer and carries a risk of lymphedema >30 %. Patients with node-positive breast cancer may consider neoadjuvant chemotherapy, which can reduce node positivity. We sought to determine if neoadjuvant chemotherapy reduced the risk of lymphedema in patients undergoing ALND for node-positive breast cancer. METHODS: The 229 patients who underwent unilateral ALND and chemotherapy were divided into two groups: 30 % (68/229) had neoadjuvant and 70 % (161/229) had adjuvant chemotherapy. Prospective arm volumes were measured via perometry preoperatively and at 3- to 7-month intervals after surgery. Lymphedema was defined as relative volume change (RVC)  $\geq 10$  %, >3 months from surgery. Kaplan-Meier curves and multivariate regression models were used to identify risk factors for lymphedema. RESULTS: Fifteen percent (10/68) of neoadjuvant patients compared with 23 % (37/161) of adjuvant patients developed RVC  $\geq 10$  % (hazard ratio = 0.76,  $p = 0.39$ ). For all patients, body mass index was significantly associated with lymphedema ( $p = 0.0003$ ). For neoadjuvant patients, residual lymph node disease after chemotherapy was associated with a ninefold greater risk of lymphedema compared to those without residual disease ( $p = 0.038$ ). CONCLUSIONS: Patients who underwent neoadjuvant chemotherapy did not have a statistically significant reduction in risk of lymphedema. Among patients who receive neoadjuvant chemotherapy, residual lymph node disease predicted a greater risk of lymphedema. These patients should be closely monitored for lymphedema and possible early intervention for the condition.

[35]

**TÍTULO / TITLE:** - Germline genetic variations in methotrexate candidate genes are associated with pharmacokinetics, toxicity and outcome in childhood acute lymphoblastic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-01-480335](https://doi.org/10.1182/blood-2013-01-480335)

**AUTORES / AUTHORS:** - Radtke S; Zolk O; Renner B; Paulides M; Zimmermann M; Moricke A; Stanulla M; Schrappe M; Langer T

**INSTITUCIÓN / INSTITUTION:** - LESS Center, University Hospital for Children and Adolescents, Department for Pediatric Oncology and Immunology, Erlangen, Germany;

**RESUMEN / SUMMARY:** - The purpose of this study was to investigate the pharmacogenetics of methotrexate (MTX) in a large cohort of pediatric patients with acute lymphoblastic leukemia (ALL) using a candidate gene approach. Therefore, 499 children with ALL from the ALL-BFM 2000 trial, who received 1996 courses of MTX at 5 g/m<sup>2</sup>, were genotyped for 8 single nucleotide polymorphisms (SNPs) in 5 candidate genes of the MTX/folate pathway. Patients' MTX pharmacokinetics, MTX toxicity, and outcome were correlated with the genotypes. The interindividual variability in MTX kinetics had a substantial genetic component between 68% and 75%. The SLCO1B1 rs4149056 variant was significantly associated with MTX kinetics. In a multiple regression model, MTX AUC<sub>0-48h</sub> increased by 26% (P=6.8x10<sup>-8</sup>) per SLCO1B1 rs4149056 C allele. MTX AUC<sub>0-48h</sub> was a significant predictor of overall toxic adverse events during MTX courses (R<sup>2</sup>=0.043, P=2.9x10<sup>-5</sup>), whereas the TYMS rs34743033 tandem repeat polymorphism was predictive of stomatitis (R<sup>2</sup>=0.018, P=0.009), a frequent side effect of high-dose MTX. Multiple Cox regression analysis revealed an association of minimal residual disease (hazard ratio 7.3; P=3.2x10<sup>-4</sup>) and MTHFR rs1801131 (hazard ratio 3.1; P=0.015) with event-free survival in the ALL-BFM 2000 study population. Genetic variations substantially influence the kinetics and response to high-dose MTX therapy in childhood ALL. (ClinicalTrials.gov: NCT00430118).

[36]

**TÍTULO / TITLE:** - Re: a phase 2 cancer chemoprevention biomarker trial of isoflavone g-2535 (genistein) in presurgical bladder cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Urol. 2013 Apr;189(4):1287-8. doi: 10.1016/j.juro.2013.01.006. Epub 2013 Jan 4.

●●Enlace al texto completo (gratis o de pago) [1016/j.juro.2013.01.006](http://1016/j.juro.2013.01.006)

**AUTORES / AUTHORS:** - Wood DP

[37]

**TÍTULO / TITLE:** - Tumor-specific cytotoxic T cells are crucial for efficacy of immunomodulatory antibodies in patients with lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 Apr 15;73(8):2381-8. doi: 10.1158/0008-5472.CAN-12-3932. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-3932](http://1158/0008-5472.CAN-12-3932)

**AUTORES / AUTHORS:** - Aerts JG; Hegmans JP

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary Diseases, Erasmus Medical Center, Rotterdam, The Netherlands. [j.aerts@erasmusmc.nl](mailto:j.aerts@erasmusmc.nl)

**RESUMEN / SUMMARY:** - There is growing evidence that activation of the immune system may be an effective treatment for patients with either small cell lung cancer or non-small cell lung cancer (NSCLC). Immunomodulatory antibodies directed against cytotoxic T cell-associated antigen 4 (CTLA-4/CD152) and programmed cell death ligand 1 (PDL1/CD274) showed clinical efficacy in patients with lung cancer. The key immune cells responsible for antitumor activity are the CTLs. The presence of these tumor-directed CTLs, both in number and functionality, is a prerequisite for the immune system to attack cancer cells. Immunomodulatory agents attempt to increase the efficacy of CTL activity. Thus, the limited number of patients who benefit from immunomodulatory antibodies may be caused by either an inadequate number or the impairment of CTL activity by the hostile environment created by the tumor. In this review, we discuss tumor-induced impairment of CTLs and experimental treatments that can stimulate T-cell responses and optimize specific CTL function. We discuss 2 types of immune cells with known suppressive capacity on CTLs that are of pivotal importance in patients with lung cancer: regulatory T cells and myeloid-derived suppressor cells.

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[38]

**TÍTULO / TITLE:** - Gradually increased Golgi protein 73 expression in the progression of benign liver diseases to precancerous lesions and hepatocellular carcinoma correlates with prognosis of patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatol Res. 2013 Jan 25. doi: 10.1111/hepr.12078.

●●Enlace al texto completo (gratis o de pago) [1111/hepr.12078](http://1111/hepr.12078)

**AUTORES / AUTHORS:** - Shan SG; Gao YT; Xu YJ; Huang Y; Zhang Q; Zhai DK; Li JB; Wang FM; Jing X; Du Z; Wang YJ

**INSTITUCIÓN / INSTITUTION:** - Third Central Clinical College of Tianjin Medical University; Hepatobiliary Surgery, Third Central Hospital of Tianjin.

**RESUMEN / SUMMARY:** - AIM: Serum Golgi protein 73 (sGP73) is a novel biomarker for hepatocellular carcinoma (HCC). However, there are few reports on the pattern of GP73 expression in the progression of benign liver diseases to precancerous lesions and HCC. This study aimed to investigate GP73 expression and its correlation with clinicopathological parameters. METHODS: Tissue GP73 (tGP73) levels were detected in specimens of group A (n = 186) including HCC, peritumoral tissue (PTL), high/low-grade hepatic atypical hyperplasia (AH), chronic hepatitis B (CHB) and normal controls (NC) by immunohistochemistry, and GP73 expression in group B (n = 159) and group C (n = 16) were detected by reverse transcription polymerase chain reaction and western blot, respectively. sGP73 levels were detected in subjects of group D (n = 287) by enzyme-linked immunoassay. RESULTS: GP73 expression increased

gradually from NC, CHB, PTL to high-grade AH and HCC at both protein and mRNA levels ( $P < 0.05$ ), while sGP73 in the HCC group was lower than in the liver cirrhosis (LC) group ( $P < 0.001$ ). Both tGP73 and sGP73 levels were negatively associated with tumor size and tumor-node-metastasis stage, and tGP73 levels were positively associated with tumor differentiation. The high-tGP73 group showed significantly better overall and disease-free survival than the low-tGP73 group ( $P = 0.008$ ,  $P = 0.018$ ). Multivariate analysis revealed that the tGP73 level was an independent prognostic factor for HCC, but not sGP73. CONCLUSION: GP73 expression pattern suggests that the regulatory mechanism of GP73 is related to the progression of chronic liver diseases. Furthermore, a high level of tGP73 is a favorable prognostic factor for HCC.

[39]

**TÍTULO / TITLE:** - Interferon-gamma production by mononuclear cells in Bacille Calmette-Guerin-revaccinated healthy volunteers predicted long-term antimycobacterial responses in a randomized controlled trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Vaccine. 2013 May 15. pii: S0264-410X(13)00552-5. doi: 10.1016/j.vaccine.2013.04.079.

●●Enlace al texto completo (gratis o de pago)

[1016/j.vaccine.2013.04.079](#)

**AUTORES / AUTHORS:** - Oliveira ES; Marinho JM; Barbosa T

**INSTITUCIÓN / INSTITUTION:** - Universidade Federal da Bahia - UFBA, Av. Reitor Miguel Calmon, s/n, Vale do Canela, 40110-902, Salvador, Bahia, Brazil; Centro de Pesquisas Goncalo Moniz - CPqGM, FIOCRUZ, Rua Waldemar Falcao 121, Candeal, 40296-710, Salvador, Bahia, Brazil. Electronic address: [evelinsoliveira@yahoo.com.br](mailto:evelinsoliveira@yahoo.com.br).

**RESUMEN / SUMMARY:** - The Bacille Calmette-Guerin (BCG) vaccine is the only vaccine currently available for tuberculosis, and it demonstrates variable efficacy against the disease. The assessment of new vaccine strategies is hindered by the small annual probability that an infected individual will develop tuberculosis, and the lack of simple and reliable surrogate markers of protection. The frequency of cytokine-producing T cells as well as the production of IFN-gamma have been disputed as surrogate markers of protection. We evaluated the evolution of these immune parameters in a population from a high burden city where BCG revaccination has been shown to result in mild protection. We found that individuals whose in vitro IFN-gamma responses to mycobacterial antigens had increased by more than 3.3-fold were more likely to maintain higher responses after 1 year and to show increased expansion of IFN-gamma-producing T lymphocytes than those with lower or null increase of IFN-gamma.

[40]

**TÍTULO / TITLE:** - A multicenter clinical study evaluating the confirmed complete molecular response rate in imatinib-treated patients with chronic phase chronic myeloid leukemia by using the international scale of real-time quantitative polymerase chain reaction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 May 28.

●●Enlace al texto completo (gratis o de pago)

[3324/haematol.2013.085167](http://3324/haematol.2013.085167)

**AUTORES / AUTHORS:** - Shinohara Y; Takahashi N; Nishiwaki K; Hino M; Kashimura M; Wakita H; Hatano Y; Hirasawa A; Nakagawa Y; Itoh K; Masuoka H; Aotsuka N; Matsuura Y; Takahara S; Sano K; Kuroki J; Hata T; Nakamae H; Mugitani A; Nakane T; Miyazaki Y; Niioka T; Miura M; Sawada K

**INSTITUCIÓN / INSTITUTION:** - Akita University, Japan;

**RESUMEN / SUMMARY:** - Achievement of complete molecular response in chronic phase chronic myeloid leukemia patients has been recognized as an important milestone in therapy cessation and treatment-free remission; therefore, the identification of predictors of complete molecular response in these patients is important. This study evaluated complete molecular response rates in imatinib-treated chronic phase chronic myeloid leukemia patients with major molecular response by using the international standardization for breakpoint cluster region-Abelson1 quantitative polymerase chain reaction. The correlation of complete molecular response with various clinical, pharmacokinetic, and immunological parameters was determined. Complete molecular response was observed in 75/152 patients (49.3%). In the univariate analysis, Sokal score, median time to major molecular response, ABCG2 421C>A, and regulatory T cells were significantly lower in chronic phase chronic myeloid leukemia patients with complete molecular response than in those without complete molecular response. In the multivariate analysis, duration of imatinib treatment (odds ratio: 1.0287, P=0.0003), time to major molecular response from imatinib therapy (odds ratio: 0.9652, P=0.0020), and ABCG2 421C/C genotype (odds ratio: 0.3953, P=0.0284) were independent predictors of complete molecular response. In contrast, NK cell number, BIM deletion polymorphisms, and plasma trough imatinib concentration were not significantly associated with achieving complete molecular response. Several predictive markers for achieving complete molecular response were identified in this study. According to our findings, some chronic myeloid leukemia patients treated with imatinib may benefit from a switch to second-generation tyrosine kinase inhibitors (ClinicalTrials.gov, UMIN000004935).

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[41]

**TÍTULO / TITLE:** - Efatutazone, an Oral PPAR-gamma Agonist, in Combination With Paclitaxel in Anaplastic Thyroid Cancer: Results of a Multicenter Phase 1 Trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Endocrinol Metab. 2013 Jun;98(6):2392-400. doi: 10.1210/jc.2013-1106. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago) [1210/jc.2013-1106](https://doi.org/10.1210/jc.2013-1106)

**AUTORES / AUTHORS:** - Smallridge RC; Copland JA; Brose MS; Wadsworth JT; Houvras Y; Menefee ME; Bible KC; Shah MH; Gramza AW; Klopper JP; Marlow LA; Heckman MG; Von Roemeling R

**INSTITUCIÓN / INSTITUTION:** - MD, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224. [smallridge.robert@mayo.edu](mailto:smallridge.robert@mayo.edu).

**RESUMEN / SUMMARY:** - Purpose: A phase 1 study was initiated to determine the safety, potential effectiveness, and maximal tolerated dose and recommended phase 2 dose of efatutazone and paclitaxel in anaplastic thyroid cancer. Experimental Design: Patients received efatutazone (0.15, 0.3, or 0.5 mg) orally twice daily and then paclitaxel every 3 weeks. Patient tolerance and outcomes were assessed, as were serum efatutazone pharmacokinetics. Results: Ten of 15 patients were women. Median age was 59 years. Seven patients received 0.15 mg of efatutazone, 6 patients received 0.3 mg, and 2 patients received 0.5 mg. One patient receiving 0.3 mg of efatutazone had a partial response from day 69 to day 175; 7 patients attained stable disease. Median times to progression were 48 and 68 days in patients receiving 0.15 mg of efatutazone and 0.3 mg of efatutazone, respectively; corresponding median survival was 98 vs 138 days. The median peak efatutazone blood level was 8.6 ng/mL for 0.15-mg dosing vs 22.0 ng/mL for 0.3-mg twice daily dosing. Ten patients had grade 3 or greater adverse events (Common Terminology Criteria for Adverse Events), with 2 of these (anemia and edema) related to efatutazone. Thirteen events of edema were reported in 8 patients, with 2 of grade 3 or greater. Eight patients had  $\geq 1$  serious adverse event, with 1 of these (anemia) attributed to efatutazone and 1 (anaphylactic reaction) related to paclitaxel. The maximal tolerated dose was not achieved. Angiopoietin-like 4 was induced by efatutazone in tissue biopsy samples of 2 patients. Conclusions: Efatutazone and paclitaxel in combination were safe and tolerated and had biologic activity.

[42]

**TÍTULO / TITLE:** - A Randomized Phase II Trial of Multi-epitope Vaccination with Melanoma Peptides for Cytotoxic T-Cells and Helper T-Cells for Patients with Metastatic Melanoma (E1602).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0002](https://doi.org/10.1158/1078-0432.CCR-13-0002)

**AUTORES / AUTHORS:** - Slingluff CL Jr; Lee S; Zhao F; Chianese-Bullock KA; Olson WC; Butterfield LH; Whiteside TL; Leming PD; Kirkwood JM

**INSTITUCIÓN / INSTITUTION:** - Surgery, University of Virginia.

**RESUMEN / SUMMARY:** - **PURPOSE:** This multicenter randomized trial was designed to evaluate whether melanoma helper peptides augment cytotoxic T-lymphocyte (CTL) responses to a melanoma vaccine and improve clinical outcome in patients with advanced melanoma. **EXPERIMENTAL DESIGN:** One hundred seventy-five patients with measurable stage IV melanoma were enrolled into 4 treatment groups, vaccinated with 12 MHC Class I-restricted melanoma peptides (12MP) to stimulate CTL (group A), plus a tetanus peptide (group B) or a mixture of 6 melanoma helper peptides (6MHP, group C) to stimulate helper T lymphocytes (HTL), or with 6MHP alone (group D), in incomplete Freund's adjuvant (IFA) plus GM-CSF. CTL responses were assessed using an in vitro stimulated IFN-gamma ELISpot assay, and HTL responses using proliferation assay. **RESULTS:** In groups A-D, respectively, CTL response rates to 12MP were 43%, 47%, 28%, and 5%, and HTL response rates to 6MHP were in 3%, 0%, 40% and 41%. Best clinical response was partial response (PR) in 7/148 evaluable patients (4.7%) without significant difference among study arms. Median overall survival (OS) was 11.8 months. Immune response to 6MHP was significantly associated with both clinical response ( $p=0.036$ ) and OS ( $p=0.004$ ). **CONCLUSIONS:** Each vaccine regimen was immunogenic, but melanoma helper peptides did not augment CTL responses to 12MP. The association of survival and immune response to 6MHP supports further investigation of helper peptide vaccines. For patients with advanced melanoma, multi-peptide vaccines should be studied in combination with other potentially synergistic active therapies.

[43]

**TÍTULO / TITLE:** - Harikumar KB, Kunnumakkara AB, Ahn KS, Anand P, Krishnan S, Guha S, Aggarwal BB. Modification of the cysteine residues in I $\kappa$ B kinase and NF- $\kappa$ B (p65) by xanthohumol leads to suppression of NF- $\kappa$ B-regulated gene products and potentiation of apoptosis in leukemia cells. *Blood*. 2009;113(9):2003-2013.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Blood*. 2013 May 2;121(18):3778. doi: 10.1182/blood-2013-03-494401.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-03-494401](http://1182/blood-2013-03-494401)

[44]

**TÍTULO / TITLE:** - CD44 regulates the apoptotic response and promotes disease development in chronic lymphocytic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 16;121(20):4126-36. doi: 10.1182/blood-2012-11-466250. Epub 2013 Apr 1.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2012-11-466250](#)

**AUTORES / AUTHORS:** - Fedorchenko O; Stiefelhagen M; Peer-Zada AA; Barthel R; Mayer P; Ecker L; Breuer A; Crispatzu G; Rosen N; Landwehr T; Lilienthal N; Mollmann M; Montesinos-Rongen M; Heukamp L; Durig J; Hallek M; Fingerle-Rowson G; Herling M

**INSTITUCIÓN / INSTITUTION:** - Department I of Internal Medicine, Center for Integrated Oncology Cologne-Bonn, and Cluster of Excellence, Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany;

**RESUMEN / SUMMARY:** - The cell-surface glycoprotein CD44 is expressed in chronic lymphocytic leukemia (CLL), but its functional role in this disease is poorly characterized. We therefore investigated the contribution of CD44 to CLL in a murine disease model, the Emicro-TCL1 transgenic mouse, and in CLL patients. Surface CD44 increased during murine CLL development. CD44 expression in human CLL was induced by stimulation with interleukin 4/soluble CD40 ligand and by stroma cell contact. Engagement of CD44 by its natural ligands, hyaluronic acid or chondroitin sulfate, protected CLL cells from apoptosis, while anti-CD44 small interfering RNAs impaired tumor cell viability. Deletion of CD44 during TCL1-driven murine leukemogenesis reduced the tumor burden in peripheral blood and spleen and led to a prolonged overall survival. The leukemic cells from these CD44 knockout animals revealed lower levels of antiapoptotic MCL1, a higher propensity to apoptosis, and a diminished B-cell receptor kinase response. The inhibitory anti-CD44 antibodies IM7 and A3D8 impaired the viability of CLL cells in suspension cultures, in stroma contact models, and in vivo via MCL1 reduction and by effector caspase activation. Taken together, CD44 expression in CLL is mediated by the tumor microenvironment. As a coreceptor, CD44 promotes leukemogenesis by regulating stimuli of MCL1 expression. Moreover, CD44 can be addressed therapeutically in CLL by specific antibodies.

[45]

**TÍTULO / TITLE:** - Correlation between eight-gene expression profiling and response to therapy of newly diagnosed multiple myeloma patients treated with thalidomide-dexamethasone incorporated into double autologous transplantation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 May 10.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1757-](#)

[6](#)

**AUTORES / AUTHORS:** - Terragna C; Renzulli M; Remondini D; Tagliafico E; Di Raimondo F; Patriarca F; Martinelli G; Roncaglia E; Masini L; Tosi P; Zamagni E; Tacchetti P; Ledda A; Brioli A; Angelucci E; Testoni N; Marzocchi G; Galieni P; Gozzetti A; Martello M; Dico F; Mancuso K; Cavo M

**INSTITUCIÓN / INSTITUTION:** - Istituto di Ematologia "Seragnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale (DIMES), Università degli Studi di Bologna, Via Massarenti, 9-40138, Bologna, Italy, [carolina.terragna@unibo.it](mailto:carolina.terragna@unibo.it).

**RESUMEN / SUMMARY:** - We performed a molecular study aimed at identifying a gene expression profile (GEP) signature predictive of attainment of at least near complete response (CR) to thalidomide-dexamethasone (TD) as induction regimen in preparation for double autologous stem cell transplantation in 112 younger patients with newly diagnosed multiple myeloma. A GEP supervised analysis was performed on a training set of 32 patients, allowing to identify 157 probe sets differentially expressed in patients with CR versus those failing CR to TD. We then generated an eight-gene GEP signature whose performance was subsequently validated in a training set of 80 patients. A correct prediction of response to TD was found in 71 % of the cases analyzed. The eight genes were downregulated in patients who achieved CR to TD. Comparisons between post-autotransplantation outcomes of the 44 non-CR-predicted patients and of the 36 CR-predicted patients showed that this latter subgroup had a statistically significant benefit in terms of higher rate of CR after autotransplant(s) and longer time to progression, event-free survival, and overall survival. These results can be an important first step to identify at diagnosis those patients who will respond more favourably to a particular treatment strategy.

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[46]

**TÍTULO / TITLE:** - Analysis of surrogate gene expression markers in peripheral blood of melanoma patients to predict treatment outcome of adjuvant pegylated interferon alpha 2b (EORTC 18991 side study).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Immunol Immunother. 2013 Apr 27.

●●Enlace al texto completo (gratis o de pago) [1007/s00262-013-1428-](https://doi.org/10.1007/s00262-013-1428-4)

[4](#)

**AUTORES / AUTHORS:** - Busse A; Raponi J; Fusi A; Suci S; Nonnenmacher A; Santinami M; Kruit WH; Testori A; Punt CJ; Dalglish AG; Spatz A; Eggermont AM; Keilholz U

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine III, Charite-CBF, Hindenburgdamm 30, 12200, Berlin, Germany, [antonia.busse@charite.de](mailto:antonia.busse@charite.de).

**RESUMEN / SUMMARY:** - We analysed mRNA levels of interferon response genes (ISG15, STAT1, CXCL10) of inhibitors of the JAK/STAT pathway (STAT3, SOCS1, SOCS3) and of cytokines (TNFalpha, IL10, TGFss1) in peripheral blood of 91 stage III melanoma patients enrolled in EORTC 18991

trial to find biomarkers indicative for disease stage and predictive for efficacy of pegylated interferon alpha-2b (PEG-IFNalpha-2b) therapy. mRNA levels were analysed at baseline and after 6 months. Univariate and multivariate analyses were performed to estimate the prognostic and predictive role of mRNA levels for distant metastasis-free survival (DMFS) and relapse-free survival (RFS). Compared to healthy controls, melanoma patients showed significantly higher TGFbeta1 mRNA levels. In a multivariate model, increasing SOCS1 and SOCS3 mRNA levels were associated with worse RFS (P = 0.02 and P = 0.04, respectively) and DMFS (P = 0.05 and P = 0.05, respectively) due to negative correlation between, respectively, SOCS1/SOCS3 mRNA levels and ulceration or Breslow thickness. No impact of PEG-IFNalpha-2b on mRNA levels was observed except for ISG15 mRNA levels, which decreased in the treatment arm (P = 0.001). It seems that patients with a decrease >60 % of ISG15 mRNA levels during 6 months PEG-IFNalpha-2b had inferior outcome.

[47]

**TÍTULO / TITLE:** - Randomized Phase II, Double-Blind, Placebo-Controlled Study of Exemestane With or Without Entinostat in Postmenopausal Women With Locally Recurrent or Metastatic Estrogen Receptor-Positive Breast Cancer Progressing on Treatment With a Nonsteroidal Aromatase Inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 6.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.43.7251](#)

**AUTORES / AUTHORS:** - Yardley DA; Ismail-Khan RR; Melichar B; Lichinitser M; Munster PN; Klein PM; Cruickshank S; Miller KD; Lee MJ; Trepel JB

**INSTITUCIÓN / INSTITUTION:** - Denise A. Yardley, Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; Roohi R. Ismail-Khan, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Bohuslav Melichar, Palacky University Medical School & Teaching Hospital, Olomouc, Czech Republic; Mikhail Lichinitser, Blokhin Russian Oncology Research Center of Russian Academy of Medical Sciences, Moscow, Russia; Pamela N. Munster, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center; Pamela M. Klein, PMK Consulting, San Francisco, CA; Pamela M. Klein, Scott Cruickshank, Syndax Pharmaceuticals, Waltham, MA; Kathy D. Miller, Indiana University School of Medicine, Indianapolis, IN; Min J. Lee, Jane B. Trepel, Center for Cancer Research, National Cancer Institute, Bethesda, MD.

**RESUMEN / SUMMARY:** - PURPOSEEntinostat is an oral isoform selective histone deacetylase inhibitor that targets resistance to hormonal therapies in estrogen receptor-positive (ER+) breast cancer. This randomized, placebo-controlled, phase II study evaluated entinostat combined with the aromatase inhibitor exemestane versus exemestane alone. PATIENTS AND METHODSPostmenopausal women with ER+ advanced breast cancer

progressing on a nonsteroidal aromatase inhibitor were randomly assigned to exemestane 25 mg daily plus entinostat 5 mg once per week (EE) or exemestane plus placebo (EP). The primary end point was progression-free survival (PFS). Blood was collected in a subset of patients for evaluation of protein lysine acetylation as a biomarker of entinostat activity. Results One hundred thirty patients were randomly assigned (EE group, n = 64; EP group, n = 66). Based on intent-to-treat analysis, treatment with EE improved median PFS to 4.3 months versus 2.3 months with EP (hazard ratio [HR], 0.73; 95% CI, 0.50 to 1.07; one-sided P = .055; two-sided P = .11 [predefined significance level of .10, one-sided]). Median overall survival was an exploratory end point and improved to 28.1 months with EE versus 19.8 months with EP (HR, 0.59; 95% CI, 0.36 to 0.97; P = .036). Fatigue and neutropenia were the most frequent grade  $\geq$  3 toxicities. Treatment discontinuation because of adverse events was higher in the EE group versus the EP group (11% v 2%). Protein lysine hyperacetylation in the EE biomarker subset was associated with prolonged PFS. CONCLUSION Entinostat added to exemestane is generally well tolerated and demonstrated activity in patients with ER+ advanced breast cancer in this signal-finding phase II study. Acetylation changes may provide an opportunity to maximize clinical benefit with entinostat. Plans for a confirmatory study are underway.

[48]

**TÍTULO / TITLE:** - Prospective Phase II Study on 5-Days Azacitidine for Treatment of Symptomatic and/or Erythropoietin Unresponsive Patients with Low/INT-1-Risk Myelodysplastic Syndromes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3540](#)

**AUTORES / AUTHORS:** - Fili C; Malagola M; Follo MY; Finelli C; Iacobucci I; Martinelli G; Cattina F; Clissa C; Candoni A; Fanin R; Gobbi M; Bocchia M; Defina M; Spedini P; Skert C; Manzoli L; Cocco L; Russo D

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Chair of Hematology, Unit of Blood Disease and Stem Cell Transplantation, University of Brescia, Brescia; Cellular Signalling Laboratory, Department of Human Anatomical Sciences, University of Bologna; Institute of Hematology and Medical Oncology "L. and A. Seragnoli", University of Bologna, Bologna; Chair and Division of Hematology, Stem Cell Transplantation Unit "Carlo Melzi", University Hospital of Udine, Udine; Department of Hematology and Oncology, University of Genova, Genova; Chair of Hematology, Hospital "Santa Maria alle Scotte," University of Siena, Siena; and Division of Hematology, Hospital "Istituti Ospitalieri" of Cremona, Cremona, Italy.

**RESUMEN / SUMMARY:** - PURPOSE: This phase II prospective study aimed to evaluate the efficacy and safety of 5-days azacytidine (5d-AZA) in patients with low-risk myelodysplastic syndromes (MDS). Second, single-nucleotide polymorphism (SNP) genetic profile and phosphoinositide-phospholipase C (PI-PLC) beta1 levels were studied to evaluate possible biologic markers able to predict the hematologic response. EXPERIMENTAL DESIGN: The study tested a lower intensity schedule of azacytidine. The treatment plan consisted of 75 mg/sqm/d subcutaneous administered for 5 days every 28 days, for a total of 8 cycles. RESULTS: Thirty-two patients were enrolled in the study. The overall response rate was 47% (15 of 32) on intention-to-treat and 58% (15 of 26) for patients completing the treatment program. In this latter group, 5 (19%) achieved complete remission (CR) and 10 (38%) had hematologic improvement, according to the International Working Group (IWG) criteria. Three patients have maintained their hematologic improvement after 37, 34, and 33 months without other treatments. Moreover, 21 and 2 of 26 cases completing 8 cycles were transfusion-dependent for red blood cells and platelets at baseline, respectively. Of these, 7 (33%) and 2 (100%) became transfusion-independent at the end of the treatment program, respectively. Grade 3-4 neutropenia occurred in 28% of patients and 4 patients died early due to infections or hemorrhage. SNP results were not significantly correlated to the clinical outcome, whereas PI-PLCbeta1 level anticipated either positive or negative clinical responses. CONCLUSIONS: 5d-AZA is safe and effective in a proportion of patients with low-risk MDS. PI-PLCbeta1 gene expression is a reliable and dynamic marker of response that can be useful to optimize azacytidine therapy. Clin Cancer Res; 1-12. ©2013 AACR.

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[49]

**TÍTULO / TITLE:** - Efficacious proteasome/HDAC inhibitor combination therapy for primary effusion lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Invest. 2013 Jun 3;123(6):2616-28. doi: 10.1172/JCI64503. Epub 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [1172/JCI64503](#)

**AUTORES / AUTHORS:** - Bhatt S; Ashlock BM; Toomey NL; Diaz LA; Mesri EA; Lossos IS; Ramos JC

**RESUMEN / SUMMARY:** - Primary effusion lymphoma (PEL) is a rare form of aggressive B cell lymphoma caused by Kaposi's sarcoma-associated herpesvirus (KSHV). Current chemotherapy approaches result in dismal outcomes, and there is an urgent need for new PEL therapies. Previously, we established, in a direct xenograft model of PEL-bearing immune-compromised mice, that treatment with the proteasome inhibitor, bortezomib (Btz), increased survival relative to that after treatment with doxorubicin. Herein, we demonstrate that the combination of Btz with the histone deacetylase (HDAC) inhibitor

suberoylanilidehydroxamic acid (SAHA, also known as vorinostat) potently reactivates KSHV lytic replication and induces PEL cell death, resulting in significantly prolonged survival of PEL-bearing mice. Importantly, Btz blocked KSHV late lytic gene expression, terminally inhibiting the full lytic cascade and production of infectious virus in vivo. Btz treatment led to caspase activation and induced DNA damage, as evidenced by the accumulation of phosphorylated gammaH2AX and p53. The addition of SAHA to Btz treatment was synergistic, as SAHA induced early acetylation of p53 and reduced interaction with its negative regulator MDM2, augmenting the effects of Btz. The eradication of KSHV-infected PEL cells without increased viremia in mice provides a strong rationale for using the proteasome/HDAC inhibitor combination therapy in PEL.

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[50]

**TÍTULO / TITLE:** - A tumor suppressor role of the Bub3 spindle checkpoint protein after apoptosis inhibition.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Biol. 2013 Apr 29;201(3):385-93. doi: 10.1083/jcb.201210018. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1083/jcb.201210018](http://1083/jcb.201210018)

**AUTORES / AUTHORS:** - Morais da Silva S; Moutinho-Santos T; Sunkel CE

**INSTITUCIÓN / INSTITUTION:** - Instituto de Biologia Molecular e Celular and 2 Instituto de Ciencias Biomedicas de Abel Salazar, Universidade do Porto, 4099 Porto, Portugal.

**RESUMEN / SUMMARY:** - Most solid tumors contain aneuploid cells, indicating that the mitotic checkpoint is permissive to the proliferation of chromosomally aberrant cells. However, mutated or altered expression of mitotic checkpoint genes accounts for a minor proportion of human tumors. We describe a *Drosophila melanogaster* tumorigenesis model derived from knocking down spindle assembly checkpoint (SAC) genes and preventing apoptosis in wing imaginal discs. Bub3-deficient tumors that were also deficient in apoptosis displayed neoplastic growth, chromosomal aneuploidy, and high proliferative potential after transplantation into adult flies. Inducing aneuploidy by knocking down CENP-E and preventing apoptosis does not induce tumorigenesis, indicating that aneuploidy is not sufficient for hyperplasia. In this system, the aneuploidy caused by a deficient SAC is not driving tumorigenesis because preventing Bub3 from binding to the kinetochore does not cause hyperproliferation. Our data suggest that Bub3 has a nonkinetochore-dependent function that is consistent with its role as a tumor suppressor.

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[51]

**TÍTULO / TITLE:** - Nomogram for predicting survival in patients with unresectable and/or metastatic urothelial cancer who are treated with cisplatin-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer. 2013 May 29. doi: 10.1002/cncr.28146.

●●Enlace al texto completo (gratis o de pago) [1002/cncr.28146](#)

**AUTORES / AUTHORS:** - Galsky MD; Moshier E; Krege S; Lin CC; Hahn N; Ecker T; Sonpavde G; Godbold J; Oh WK; Bamias A

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, New York.

**RESUMEN / SUMMARY:** - BACKGROUND: The current study was conducted to develop a pretreatment prognostic model for patients with unresectable and/or metastatic urothelial cancer who were treated with first-line, cisplatin-based chemotherapy. METHODS: Individual data were pooled from 399 patients who were enrolled on 8 phase 2 and 3 trials evaluating cisplatin-based, first-line chemotherapy in patients with metastatic urothelial carcinoma. Variables selected for inclusion in the model were combined in a Cox proportional hazards model to produce a points-based nomogram with which to predict the median, 1-year, 2-year, and 5-year survival. The nomogram was validated externally using data from a randomized trial of the combination of methotrexate, vinblastine, doxorubicin plus cisplatin versus docetaxel plus cisplatin. RESULTS: The median survival of the development cohort was 13.8 months (95% confidence interval, 12.1 months-16.0 months); 68.2% of the patients had died at the time of last follow-up. On multivariable analysis, the number of visceral metastatic sites, Eastern Cooperative Oncology Group performance status, and leukocyte count were each found to be associated with overall survival ( $P < .05$ ), whereas the site of the primary tumor and the presence of lymph node metastases were not. All 5 variables were included in the nomogram. When subjected to internal validation, the nomogram achieved a bootstrap-corrected concordance index of 0.626. When applied to the external validation cohort, the nomogram achieved a concordance index of 0.634. Calibration plots suggested that the nomogram was well calibrated for all predictions. CONCLUSIONS: Based on routinely measured pretreatment variables, a nomogram was constructed that predicts survival in patients with unresectable and/or metastatic urothelial cancer who are treated with cisplatin-based chemotherapy. This model may be useful in patient counseling and clinical trial design. Cancer 2013. © 2013 American Cancer Society.

[52]

**TÍTULO / TITLE:** - Impact of polymorphisms in drug pathway genes on disease-free survival in adults with acute myeloid leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hum Genet. 2013 May 16. doi: 10.1038/jhg.2013.38.

●●Enlace al texto completo (gratis o de pago) [1038/jhg.2013.38](https://doi.org/10.1038/jhg.2013.38)

**AUTORES / AUTHORS:** - Yee SW; Mefford JA; Singh N; Percival ME; Stecula A; Yang K; Witte JS; Takahashi A; Kubo M; Matsuda K; Giacomini KM; Andreadis C

**INSTITUCIÓN / INSTITUTION:** - Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA, USA.

**RESUMEN / SUMMARY:** - Acute myeloid leukemia (AML) is a clinically heterogeneous disease, with a 5-year disease-free survival (DFS) ranging from under 10% to over 70% for distinct groups of patients. At our institution, cytarabine, etoposide and busulfan are used in first or second remission patients treated with a two-step approach to autologous stem cell transplantation (ASCT). In this study, we tested the hypothesis that polymorphisms in the pharmacokinetic and pharmacodynamic pathway genes of these drugs are associated with DFS in AML patients. A total of 1659 variants in 42 genes were analyzed for their association with DFS using a Cox-proportional hazards model. One hundred and fifty-four genetically European patients were used for the primary analysis. An intronic single nucleotide polymorphism (SNP) in ABCC3 (rs4148405) was associated with a significantly shorter DFS (hazard ratios (HR)=3.2, P=5.6 x 10<sup>-6</sup>) in our primary cohort. In addition, a SNP in the GSTM1-GSTM5 locus, rs3754446, was significantly associated with a shorter DFS in all patients (HR=1.8, P=0.001 for 154 European ancestry; HR=1.7, P=0.028 for 125 non-European patients). Thus, for the first time, genetic variants in drug pathway genes are shown to be associated with DFS in AML patients treated with chemotherapy-based autologous ASCT. Journal of Human Genetics advance online publication, 16 May 2013; doi:10.1038/jhg.2013.38.

[53]

**TÍTULO / TITLE:** - HER2/CEP17 ratio and HER2 immunohistochemistry predict clinical outcome after first-line trastuzumab plus taxane chemotherapy in patients with HER2 fluorescence in situ hybridization-positive metastatic breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2174-](https://doi.org/10.1007/s00280-013-2174-1)

[1](#)

**AUTORES / AUTHORS:** - Kim JW; Kim JH; Im SA; Kim YJ; Han HS; Kim JS; Lee KH; Kim TY; Han SW; Jeon YK; Oh DY; Kim TY; Park IA

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, 110-744, Korea.

**RESUMEN / SUMMARY:** - PURPOSE: This study aimed to elucidate the clinical implication of human epidermal growth factor receptor 2/centromeric probe for

chromosome 17 (HER2/CEP17) ratio and HER2 immunohistochemistry (IHC) results in patients with HER2 fluorescence in situ hybridization (FISH)-positive metastatic breast cancer (MBC) who received first-line trastuzumab plus taxane chemotherapy. METHODS: Using clinical data of patients with HER2 FISH-positive MBC who received first-line trastuzumab plus taxane chemotherapy, we analyzed the clinical outcome according to the HER2/CEP17 ratio and HER2 IHC analysis. RESULTS: Fifty-two women were analyzed. The median age was 50 years (range 27-69 years). Patients with a HER2/CEP17 ratio  $\geq 3.0$  had significantly longer progression-free survival (PFS) (17.2 vs. 7.4 months;  $p = 0.002$ ) with a tendency toward higher response rate (RR) ( $p = 0.325$ ) and longer overall survival (OS) ( $p = 0.129$ ). Patients with HER2 IHC 1+ had significantly shorter OS (14.0 vs. 42.4 months;  $p = 0.013$ ) along with a tendency toward lower RR ( $p = 0.068$ ) and shorter PFS ( $p = 0.220$ ). In the multivariate analysis, HER2/CEP17 ratio  $< 3.0$  ( $p = 0.004$ ) and Eastern Cooperative Oncology Group (ECOG) PS 2 ( $p = 0.015$ ) were significant factors for shorter PFS, and HER2 IHC 1+ ( $p = 0.015$ ) and ECOG PS 2 ( $p = 0.036$ ) were significant factors for poor OS. CONCLUSIONS: Our data support that HER2/CEP17 ratios and HER2 IHC scores may predict clinical outcome after first-line trastuzumab plus taxane chemotherapy in patients with HER2 FISH-positive MBC.

[54]

**TÍTULO / TITLE:** - Pronecrotic mixed lineage kinase domain-like protein expression is a prognostic biomarker in patients with early-stage resected pancreatic adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer. 2013 May 29. doi: 10.1002/cncr.28144.

●●Enlace al texto completo (gratis o de pago) [1002/cncr.28144](#)

**AUTORES / AUTHORS:** - Colbert LE; Fisher SB; Hardy CW; Hall WA; Saka B; Shelton JW; Petrova AV; Warren MD; Pantazides BG; Gandhi K; Kowalski J; Kooby DA; El-Rayes BF; Staley CA 3rd; Adsay NV; Curran WJ Jr; Landry JC; Maitzel SK; Yu DS

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia.

**RESUMEN / SUMMARY:** - BACKGROUND: Mixed lineage kinase domain-like protein (MLKL) is a necrosome component mediating programmed necrosis that may be an important determinant of cancer cell death. The goal of the current study was to evaluate the prognostic value of MLKL expression in patients with pancreatic adenocarcinoma (PAC). METHODS: Tissue from 80 patients was collected from a prospectively maintained database of patients with PAC who underwent pancreaticoduodenectomy between January 2000 and October 2008. Immunohistochemistry analysis was performed and scored using an established scoring system. Kaplan-Meier survival curves were generated for

recurrence-free survival (RFS) and overall survival (OS) for all patients and for patients receiving adjuvant chemotherapy. MLKL scores were correlated with RFS and OS using univariate and multivariate Cox regression analyses incorporating clinically relevant covariates. RESULTS: The median age of the patients was 63 years and 53% were men. Low MLKL expression was associated with decreased OS (6 months vs 17 months; P = .006). In the subset of 59 patients who received adjuvant chemotherapy, low MLKL expression was associated with decreased RFS (5 months vs 15 months; P = .006) and decreased OS (6 months vs 19 months; P < .0001). On multivariate analysis, low MLKL expression was associated with poor OS in all patients (hazards ratio, 4.6 [95% confidence interval, 1.6-13.8]; P = .006) and in patients receiving adjuvant chemotherapy (hazards ratio, 8.1 [95% confidence interval, 2.2-29.2]; P = .002). CONCLUSIONS: Low expression of MLKL is associated with decreased OS in patients with resected PAC and decreased RFS and OS in the subset of patients with resected PAC who receive adjuvant chemotherapy. The use of this biomarker in patients with PAC may provide important prognostic information. Cancer 2013. © 2013 American Cancer Society.

[55]

**TÍTULO / TITLE:** - Prognostic factors for survival in 1059 patients treated with sunitinib for metastatic renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 May 21. doi: 10.1038/bjc.2013.236.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.236](#)

**AUTORES / AUTHORS:** - Motzer RJ; Escudier B; Bukowski R; Rini BI; Hutson TE; Barrios CH; Lin X; Fly K; Matczak E; Gore ME

**INSTITUCIÓN / INSTITUTION:** - Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, 10021 New York, NY, USA.

**RESUMEN / SUMMARY:** - Background:Prognostic factors for progression-free survival (PFS), overall survival (OS), and long-term OS (>/=30 months) were investigated in sunitinib-treated patients with metastatic renal cell carcinoma (RCC).Methods:Data were pooled from 1059 patients in six trials. Baseline variables, including ethnicity, were analysed for prognostic significance by Cox proportional-hazards model.Results:Median PFS and OS were 9.7 and 23.4 months, respectively. Multivariate analysis of PFS and OS identified independent predictors, including ethnic origin, Eastern Cooperative Oncology Group performance status, time from diagnosis to treatment, prior cytokine use, haemoglobin, lactate dehydrogenase, corrected calcium, neutrophils, platelets, and bone metastases (OS only). Characteristics of long-term survivors (n=215, 20%) differed from those of non-long-term survivors; independent predictors of long-term OS included ethnic origin, bone metastases, and corrected calcium. There were no differences in PFS (10.5 vs 7.2 months; P=0.1006) or OS (23.8 vs 21.4 months; P=0.2135) in white vs Asian patients; however, there were

significant differences in PFS (10.5 vs 5.7 months;  $P < 0.001$ ) and OS (23.8 vs 17.4 months;  $P = 0.0319$ ) in white vs non-white, non-Asian patients. Conclusion: These analyses identified risk factors to survival with sunitinib, including potential ethnic-based differences, and validated risk factors previously reported in advanced RCC. British Journal of Cancer advance online publication, 21 May 2013; doi:10.1038/bjc.2013.236 [www.bjcancer.com](http://www.bjcancer.com).

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[56]

**TÍTULO / TITLE:** - Usefulness of circulating tumor cells after preliminary chemotherapy for prediction of response to further anticancer therapy in patients with initially unresectable metastatic colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1769-72.

**AUTORES / AUTHORS:** - Neki K; Kawahara H; Watanabe K; Toyama Y; Akiba T; Yanaga K

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Kashiwa Hospital, Jikei University School of Medicine, Kashiwashi, Chiba, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND/AIM: The aim of this study was to evaluate the usefulness of circulating tumor cells (CTCs) after preliminary chemotherapy for prediction of response to further anticancer therapy in patients with initially unresectable metastatic colorectal cancer. PATIENTS AND METHODS: CTCs from 14 consecutive patients with Kirsten rat sarcoma viral oncogene homolog (KRAS) wild-type colorectal cancer with synchronous or metachronous unresectable metastatic lesions were measured using the CellSearch system between January 2009 and December 2011. CTCs were measured before and after chemotherapy. The regimen consisted of four courses (three months) of oxaliplatin with oral S-1 (SOX) + panitumumab. RESULTS: Ten (71%) out of all patients had no detectable CTCs after chemotherapy. Eight out of these ten patients received further chemotherapy, and liver metastases were completely resected in the other two patients; none of these patients died of cancer within a year after starting chemotherapy. The remaining four patients with CTCs continued to have CTCs after chemotherapy, and all four of these patients died of cancer within eight months after starting chemotherapy. The prognosis of the patients who had no detectable CTCs after the chemotherapy was significantly better than that of those who had CTCs even after the chemotherapy ( $p < 0.01$ ). CONCLUSION: CTCs after preliminary chemotherapy may be useful in predicting the response to further anticancer therapy.

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[57]

**TÍTULO / TITLE:** - C-reactive protein is an indicator of serum infliximab level in predicting loss of response in patients with Crohn's disease.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gastroenterol. 2013 Apr 20.

●●Enlace al texto completo (gratis o de pago) [1007/s00535-013-0807-](#)

[0](#)

**AUTORES / AUTHORS:** - Hibi T; Sakuraba A; Watanabe M; Motoya S; Ito H; Sato N; Yoshinari T; Motegi K; Kinouchi Y; Takazoe M; Suzuki Y; Matsumoto T; Kawakami K; Matsumoto T; Hirata I; Tanaka S; Ashida T; Matsui T

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan, [thibi@z5.keio.jp](mailto:thibi@z5.keio.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The ability of serum infliximab level to predict clinical outcome in infliximab therapy in Crohn's disease is unclear. Here, we aimed to clarify the correlation between the timing of loss of response (LOR) to treatment and a decrease in serum infliximab level, and, in addition, to identify an indicator of infliximab level. METHODS: The study used data from a previous clinical study of infliximab for Crohn's disease, in which infliximab was initially given at 0, 2, 6 weeks at 5 mg/kg, and then at 8-week intervals to 62 week-10 responders. Of these 62, here we analysed data from 57 in whom Crohn's disease activity index and serum infliximab level were evaluated at week 14. RESULTS: Twelve patients showed a clinical response despite an infliximab level <1 µg/mL at week 14; of these, 8 (67 %) experienced LOR by week 54. A decrease in infliximab level preceded LOR in 6 (75 %). In receiver operating characteristic curve analysis, C-reactive protein (CRP) showed better performance in detecting an infliximab level <1 µg/mL. Infliximab level was <1 µg/mL in 60-80 % of patients with CRP >0.5 mg/dL. Time to LOR (median: 22.0 weeks) was significantly longer than that to a decrease in infliximab level to <1 µg/mL (14.0 weeks, p < 0.05) or to an increase in CRP to >0.5 mg/dL (14.0 weeks, p < 0.01). CONCLUSIONS: A decrease in serum infliximab level preceded LOR, and was easily detected by an increase in CRP. The CRP may be an indicator of serum infliximab level in predicting LOR.

[58]

**TÍTULO / TITLE:** - Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Brain Behav Immun. 2013 Jul;31:205-15. doi: 10.1016/j.bbi.2013.04.004. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbi.2013.04.004](#)

**AUTORES / AUTHORS:** - Mehta D; Raison CL; Woolwine BJ; Haroon E; Binder EB; Miller AH; Felger JC

**INSTITUCIÓN / INSTITUTION:** - Max Planck Institute of Psychiatry, Munich, Germany.

**RESUMEN / SUMMARY:** - The tumor necrosis factor (TNF) antagonist infliximab was recently found to reduce depressive symptoms in patients with increased baseline inflammation as reflected by a plasma C-reactive protein concentration >5mg/L. To further explore predictors and targets of response to infliximab, differential gene expression was examined in peripheral blood mononuclear cells from infliximab responders (n=13) versus non-responders (n=14) compared to placebo at baseline and 6h, 24h, and 2weeks after the first infliximab infusion. Treatment response was defined as 50% reduction in depressive symptoms at any point during the 12-week trial. One-hundred-forty-eight gene transcripts were significantly associated (1.2-fold, adjusted p0.01) with response to infliximab and were distinct from placebo responders. Transcripts predictive of infliximab response were associated with gluconeogenesis and cholesterol transport, and were enriched in a network regulated by hepatocyte nuclear factor (HNF)4-alpha, a transcription factor involved in gluconeogenesis and cholesterol and lipid homeostasis. Of the 148 transcripts differentially expressed at baseline, 48% were significantly regulated over time in infliximab responders, including genes related to gluconeogenesis and the HNF4-alpha network, indicating that these predictive genes were responsive to infliximab. Responders also demonstrated inhibition of genes related to apoptosis through TNF signaling at 6h and 24h after infusion. Transcripts down-regulated in responders 2weeks after infliximab were related to innate immune signaling and nuclear factor-kappa B. Thus, baseline transcriptional signatures reflective of alterations in glucose and lipid metabolism predicted antidepressant response to infliximab, and infliximab response involved regulation of metabolic genes and inhibition of genes related to innate immune activation.

[59]

**TÍTULO / TITLE:** - Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 2.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-03-493197](https://doi.org/10.1182/blood-2013-03-493197)

**AUTORES / AUTHORS:** - Dinardo CD; Propert KJ; Loren AW; Paietta E; Sun Z; Levine RL; Straley KS; Yen K; Patel JP; Agresta S; Abdel-Wahab O; Perl AE; Litzow MR; Rowe JM; Lazarus HM; Fernandez HF; Margolis DJ; Tallman MS; Luger SM; Carroll M

**INSTITUCIÓN / INSTITUTION:** - University of Pennsylvania, Philadelphia, PA, United States;

**RESUMEN / SUMMARY:** - Cancer-associated IDH mutations produce the metabolite 2-hydroxyglutarate (2HG), but the clinical utility of serum 2HG measurements is not established. We studied whether 2HG measurements in

AML patients correlate with IDH mutations, and whether diagnostic or remission 2HG measurements predict survival. Serum from 223 adults with de novo AML (62 IDH-mutated, 161 wild-type) were analyzed for 2HG concentration by reverse-phase liquid chromatography-mass spectrometry (LC-MS). Pretreatment 2HG levels ranged from 10 to 30,000ng/ml and were elevated in IDH-mutants (median 3004ng/ml), compared to the wild-type cohort (median 61ng/ml) ( $p < 0.0005$ ). 2HG levels did not differ among IDH1 or IDH2 allelic variants. In receiver operating curve (ROC) analysis, a discriminatory level of 700ng/ml segregated patients with and without IDH mutations with 86.9% sensitivity and 90.7% specificity. On repeat mutational analysis of 13 IDH wild-type samples with 2HG levels  $> 700$ ng/ml, IDH mutations were identified in nine samples. IDH-mutant patients with 2HG levels  $> 200$ ng/ml at complete remission experienced shorter overall survival compared to those with 2HG  $< 200$ ng/ml (HR 3.9,  $p = 0.02$ ). We establish a firm association between IDH mutations and elevated serum 2HG concentration in AML. These data confirm that serum measurement of an oncometabolite provides useful diagnostic and prognostic information, and can improve patient selection for IDH-targeted therapies.

[60]

**TÍTULO / TITLE:** - DJ-1 protein expression as a predictor of pathological complete remission after neoadjuvant chemotherapy in breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 May;139(1):51-9. doi: 10.1007/s10549-013-2523-0. Epub 2013 Apr 17.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2523-](#)

[0](#)

**AUTORES / AUTHORS:** - Kawate T; Iwaya K; Kikuchi R; Kaise H; Oda M; Sato E; Hiroi S; Matsubara O; Kohno N

**INSTITUCIÓN / INSTITUTION:** - Department of Basic Pathology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama, 359-8513, Japan.

**RESUMEN / SUMMARY:** - Parkinson's disease is associated with DJ-1/Parkinson protein 7 dysfunction. In contrast, hyperactivity of DJ-1 increases the resistance of cancer cells to apoptosis. Recent genetic studies showed that, in addition to apoptosis pathways, DJ-1 is also involved in cellular defense against reactive oxygen species. The activity of apoptotic and cellular defense pathways is key in determining drug sensitivity. DJ-1 overexpression is associated with various cancers. However, we previously found that there were approximately 50 % patients with breast cancers that expressed low levels of DJ-1 protein, despite mRNA upregulation. Furthermore, low DJ-1 expression was a significant predictor of poor clinical outcome in these patients. This study aimed to determine the association between low DJ-1 protein expression and pathological complete remission (pCR) after neoadjuvant chemotherapy in breast cancer patients. Expression of DJ-1 in pre-therapeutic needle biopsies

and surgical specimens obtained from 205 breast cancer cases that received neoadjuvant chemotherapy was determined using immunohistochemistry and in situ hybridization. Chemotherapy comprised epirubicin/cyclophosphamide taxane-based regimens with or without the inclusion of trastuzumab. Univariate and multivariate analyses were used to evaluate the predictive value of DJ-1 on pCR. Low DJ-1 protein expression was detected in 45.3 % (93/205) of all breast cancer cases and in 79.6 % (39/49) of pCR cases, irrespective of maintained mRNA levels. DJ-1 expression [hazard ratio (HR): 1.36; 95 % confidence interval (CI): 1.01-1.84] and HER2 status (HR: 0.84; 95 % CI: 0.62-1.14), in contrast to histological grade, hormone receptors status, Ki-67 labeling index, and intrinsic subtype, were significant predictors of pCR. Low DJ-1 expression predicted pCR in luminal A (P = 0.0004), luminal B (P = 0.0194), and triple negative (P = 0.0143) subtypes breast cancer patients and in patients receiving additional trastuzumab treatment (P = 0.008). In conclusion, low DJ-1 protein expression is a significant predictor of pCR after neoadjuvant chemotherapy in breast cancer patients.

[61]

**TÍTULO / TITLE:** - Combination of protein coding and non-coding gene expression as a robust prognostic classifier in stage I lung adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 May 2.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-0031](#)

**AUTORES / AUTHORS:** - Akagi I; Okayama H; Schetter AJ; Robles AI; Kohno T; Bowman ED; Kazandjian D; Welsh JA; Oue N; Saito M; Miyashita M; Uchida E; Takizawa T; Takenoshita S; Skaug V; Mollerup S; Haugen A; Yokota J; Harris CC

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Human Carcinogenesis, National Cancer Institute.

**RESUMEN / SUMMARY:** - Prognostic tests for early stage lung cancer patients may provide needed guidance on postoperative surveillance and therapeutic decisions. We used a novel strategy to develop and validate a prognostic classifier for early stage lung cancer. Specifically, we focused on 42 genes with roles in lung cancer or cancer prognosis. Expression of these biologically relevant genes and their association with relapse-free survival were evaluated using microarray data from 148 stage I lung adenocarcinoma patients. Seven genes associated with relapse-free survival were further examined by quantitative RT-PCR in 291 lung adenocarcinoma tissues from Japan, the United States and Norway. Only BRCA1, HIF1A, DLC1, and XPO1 were each significantly associated with prognosis in the Japan and US/Norway cohorts. A Cox regression-based classifier was developed using these four genes on the Japan cohort and validated in stage I lung adenocarcinoma from the

US/Norway cohort and three publically available lung adenocarcinoma expression profiling datasets. The results suggests that the classifier is robust across ethnically and geographically diverse populations regardless of the technology used to measure gene expression. We evaluated the combination of the four-gene classifier with microRNA miR-21 (MIR21) expression and found that the combination improved associations with prognosis, which were significant in stratified analyses on stage IA and stage IB patients. Thus, the four coding gene classifier, alone or with miR-21 expression, may provide a clinically useful tool to identify high risk patients and guide recommendations regarding adjuvant therapy and postoperative surveillance of stage I lung adenocarcinoma patients.

[62]

**TÍTULO / TITLE:** - Threshold Levels of ABL Tyrosine Kinase Inhibitors Retained in Chronic Myeloid Leukemia Cells Determine Their Commitment to Apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 Jun 1;73(11):3356-3370. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-3904](#)

**AUTORES / AUTHORS:** - O'Hare T; Eide CA; Agarwal A; Adrian LT; Zabriskie MS; Mackenzie RJ; Latocha DH; Johnson KJ; You H; Luo J; Riddle SM; Marks BD; Vogel KW; Koop DR; Apgar J; Tyner JW; Deininger MW; Druker BJ

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Division of Hematology and Hematologic Malignancies, University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah; Division of Hematology and Medical Oncology; Departments of Physiology and Pharmacology and Cell and Developmental Biology; Bioanalytical Shared Resource/Pharmacokinetics Core; Knight Cancer Institute, Oregon Health & Science University; Howard Hughes Medical Institute, Portland, Oregon; Life Technologies, Madison, Wisconsin; and BD Biosciences, San Diego, California.

**RESUMEN / SUMMARY:** - The imatinib paradigm in chronic myelogenous leukemia (CML) established continuous BCR-ABL inhibition as a design principle for ABL tyrosine kinase inhibitors (TKI). However, clinical responses seen in patients treated with the ABL TKI dasatinib despite its much shorter plasma half-life and the apparent rapid restoration of BCR-ABL signaling activity following once-daily dosing suggested acute, potent inhibition of kinase activity may be sufficient to irrevocably commit CML cells to apoptosis. To determine the specific requirements for ABL TKI-induced CML cell death for a panel of clinically important ABL TKIs (imatinib, nilotinib, dasatinib, ponatinib, and DCC-2036), we interrogated response of CML cell lines and primary CML cells following acute drug exposure using intracellular fluorescence-activated cell sorting and immunoblot analyses of BCR-ABL signaling, apoptosis

measurements, liquid chromatography/tandem mass spectrometry of intracellular drug levels, and biochemical TKI dissociation studies. Importantly, significant intracellular TKI stores were detected following drug washout, levels of which tracked with onset of apoptosis and incomplete return of BCR-ABL signaling, particularly pSTAT5, to baseline. Among TKIs tested, ponatinib showed the most robust capacity for apoptotic commitment showing sustained suppression of BCR-ABL signaling even at low intracellular levels following extensive washout, consistent with high-affinity binding and slow dissociation from ABL kinase. Together, our findings suggest commitment of CML cells to apoptosis requires protracted incomplete restoration of BCR-ABL signaling mediated by intracellular retention of TKIs above a quantifiable threshold. These studies refine our understanding of apoptotic commitment in CML cells and highlight parameters important to design of therapeutic kinase inhibitors for CML and other malignancies. *Cancer Res*; 73(11); 3356-70. ©2013 AACR.

[63]

**TÍTULO / TITLE:** - Prognostic implication of mucinous histology in colorectal cancer patients treated with adjuvant FOLFOX chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Br J Cancer*. 2013 May 28;108(10):1978-84. doi: 10.1038/bjc.2013.232. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.232](http://1038/bjc.2013.232)

**AUTORES / AUTHORS:** - Lee DW; Han SW; Lee HJ; Rhee YY; Bae JM; Cho NY; Lee KH; Kim TY; Oh DY; Im SA; Bang YJ; Jeong SY; Park KJ; Park JG; Kang GH; Kim TY

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea.

**RESUMEN / SUMMARY:** - Background: There have been controversies in prognostic impact of mucinous histology on colorectal cancer, and its implication in patients treated with adjuvant 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) is unclear. Methods: Stage II and III colorectal cancer patients who underwent curative resection followed by adjuvant FOLFOX were included. Patients were grouped according to the mucinous content: >50%, mucinous adenocarcinoma (MAC); <50%, adenocarcinoma with intermediated mucinous component (AIM); and without any mucinous component, non-MAC (NMA). Clinicopathological features and disease-free survival (DFS) were compared. Results: Among a total of 521 patients, 27 patients (5.2%) had MAC, 41 patients (7.9%) had AIM, and 453 patients (86.9%) had NMA. Mucinous adenocarcinoma and AIM had higher frequency of proximal location and microsatellite instability, but lower frequency of angiolymphatic invasion. Disease-free survival was significantly worse in the MAC compared with NMA (3-year DFS 57% and 86%, respectively;  $P < 0.001$ ) and AIM (3-year DFS 87%,  $P = 0.01$  vs MAC). Multivariate analysis revealed MAC as an independent

negative prognostic factor of DFS (adjusted hazard ratio 7.96, 95% confidence interval 3.76-16.8). Conclusion: Adenocarcinoma with intermediated mucinous component and MAC have distinct clinicopathological features compared with NMA. Mucinous adenocarcinoma has an adverse prognostic impact on stage II or III colorectal cancer treated with adjuvant FOLFOX.

[64]

**TÍTULO / TITLE:** - Polyclonal immune activation and marrow plasmacytosis in multiple myeloma patients receiving long-term lenalidomide therapy: incidence and prognostic significance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leukemia. 2013 Apr 23. doi: 10.1038/leu.2013.126.

●●Enlace al texto completo (gratis o de pago) [1038/leu.2013.126](#)

**AUTORES / AUTHORS:** - Zamarin D; Devlin SM; Arcila ME; Landau H; Lesokhin A; Lendvai N; Chung DJ; Chimento D; Wetz J; Babu D; Giral S; Hassoun H

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Division of Hematologic Malignancies, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA.

[65]

**TÍTULO / TITLE:** - Complete remission of acute promyelocytic leukemia in a very elderly patient after treatment with low dose arsenic trioxide and sequential retinoic acid: a case report.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 May 30.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1791-](#)

[4](#)

**AUTORES / AUTHORS:** - Lin J; Zhu H; Li S; Fan H; Lu X

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatric Hematology, Chinese PLA General Hospital, Haidian District, Beijing, China.

[66]

**TÍTULO / TITLE:** - Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 23;121(21):4287-94. doi: 10.1182/blood-2012-12-471680. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2012-12-](#)

[471680](#)

**AUTORES / AUTHORS:** - Klepin HD; Geiger AM; Tooze JA; Kritchevsky SB; Williamson JD; Pardee TS; Ellis LR; Powell BL

**INSTITUCIÓN / INSTITUTION:** - Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC; and.

**RESUMEN / SUMMARY:** - We investigated the predictive value of geriatric assessment (GA) on overall survival (OS) for older adults with acute myelogenous leukemia (AML). Consecutive patients  $\geq 60$  years with newly diagnosed AML and planned intensive chemotherapy were enrolled at a single institution. Pretreatment GA included evaluation of cognition, depression, distress, physical function (PF) (self-reported and objectively measured), and comorbidity. Objective PF was assessed using the Short Physical Performance Battery (SPPB, timed 4-m walk, chair stands, standing balance) and grip strength. Cox proportional hazards models were fit for each GA measure as a predictor of OS. Among 74 patients, the mean age was 70 years, and 78.4% had an Eastern Cooperative Oncology Group (ECOG) score  $\leq 1$ . OS was significantly shorter for participants who screened positive for impairment in cognition and objectively measured PF. Adjusting for age, gender, ECOG score, cytogenetic risk group, myelodysplastic syndrome, and hemoglobin, impaired cognition (Modified Mini-Mental State Exam  $< 77$ ) and impaired objective PF (SPPB  $< 9$ ) were associated with worse OS. GA methods, with a focus on cognitive and PF, improve risk stratification and may inform interventions to improve outcomes for older AML patients.

[67]

**TÍTULO / TITLE:** - Can we identify predictive biomarkers for antiangiogenic therapy of cancer using mathematical modeling?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Natl Cancer Inst. 2013 Jun 5;105(11):762-5. doi: 10.1093/jnci/djt114. Epub 2013 May 13.

●●Enlace al texto completo (gratis o de pago) [1093/jnci/djt114](#)

**AUTORES / AUTHORS:** - Duda DG; Munn LL; Jain RK

**INSTITUCIÓN / INSTITUTION:** - Affiliations of authors: Steele Laboratory, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA (DGD, LLM, RKJ).

[68]

**TÍTULO / TITLE:** - Clinical Significance of ABCG2 Haplotype-tagging Single Nucleotide Polymorphisms in Patients With Unresectable Non-Small Cell Lung Cancer Treated With First-line Platinum-based Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Clin Oncol. 2013 May 17.

●●Enlace al texto completo (gratis o de pago)

[1097/COC.0b013e318297f333](#)

**AUTORES / AUTHORS:** - Kim SH; Kim MJ; Cho YJ; Jeong YY; Kim HC; Lee JD; Hwang YS; Kim IS; Lee S; Oh SY; Ling H; Lee GW

**INSTITUCIÓN / INSTITUTION:** - \*Department of Internal Medicine, Division of Hematology and Medical Oncology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon daggerDepartment of Internal Medicine, Division of Hematology-Oncology, Gyeongsang National University School of Medicine double daggerDepartment of Internal Medicine, Division of Pulmonology, Gyeongsang National University Hospital, Jinju section signDepartment of Laboratory Medicine, Pusan National University School of Medicine, Busan parallelDepartment of Internal Medicine, Division of Hematology-Oncology, Dong-A University Medical Center, Busan, Republic of Korea paragraph signDepartment of Experimental Therapeutics, M.D. Anderson Cancer Center, University of Texas, Houston, TX.

**RESUMEN / SUMMARY:** - **OBJECTIVES::** The ATP-binding cassette (ABC) ABCG2, involved in multidrug resistance (MDR) in cancer cells, plays an integral role in drug resistance. Single nucleotide polymorphisms (SNPs) have been identified in many MDR-associated ABC genes that seem to influence drug sensitivity/resistance through various mechanisms. Therefore, we investigated whether ABCG2 haplotype-tagging SNPs (htSNPs) were associated with clinical outcomes in patients with unresectable non-small cell lung cancer (NSCLC) treated with front-line platinum-based chemotherapy. **PATIENTS AND METHODS::** We genotyped 4 ABCG2 htSNPs for 129 unresectable NSCLC cases treated with first-line platinum-based chemotherapy. Clinical characteristics, treatment outcomes, and predictive value of the htSNPs in patient response, survival, and adverse events related to platinum-based chemotherapy were analyzed according to each ABCG2 htSNP using the chi test, Kaplan-Meier method, and Cox proportional hazard model. **RESULTS::** The rs2725264 was significantly related to overall survival (OS) ( $P=0.018$ , log-rank test). The median survival duration (in months) for patients with the rs2725264 T/T, T/C, and C/C genotypes was 35.75 [95% confidence interval (CI), 24.25-47.25], 34.25 [hazard ratio (HR) 1.27 (0.68 to 2.35); 95% CI, 27.16-41.34], and 14.89 [HR 3.22 (1.26 to 8.24), 95% CI, 13.86-15.92], respectively. The rs2725264 was identified as an independent factor by Cox proportional hazard model analysis ( $P=0.028$ ). In the taxane-based groups, OS was associated with rs2725264 ( $P=0.041$ ), whereas in the gemcitabine-based groups, OS was associated with rs4148149 ( $P=0.014$ ). **CONCLUSIONS::** Our data suggest ABCG2 htSNPs rs2725264 (overall group and taxane-platinum combination group) and rs4148149 (gemcitabine-platinum combination group) were associated with OS in unresectable NSCLC patients treated with first-line platinum-based chemotherapy. Thus, the ABCG2 htSNP rs2725264 may be independently associated with OS in unresectable NSCLC patients treated with first-line platinum-based chemotherapy.

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[69]

**TÍTULO / TITLE:** - CD30, another useful predictor of survival in DLBCL?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 Apr 4;121(14):2582-3. doi: 10.1182/blood-2013-02-481978.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-02-481978](#)

**AUTORES / AUTHORS:** - Chan WC

**INSTITUCIÓN / INSTITUTION:** - University of Nebraska Medical Center, USA.

[70]

**TÍTULO / TITLE:** - The BCR-ABL T315I mutation compromises survival in chronic phase chronic myelogenous leukemia patients resistant to tyrosine kinase inhibitors, in a matched pair analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [3324/haematol.2012.080234](#)

**AUTORES / AUTHORS:** - Nicolini FE; Ibrahim AR; Soverini S; Martinelli G; Muller MC; Hochhaus A; Dufva IH; Kim DW; Cortes J; Mauro MJ; Chuah C; Labussiere H; Morisset S; Roche-Lestienne C; Lippert E; Hayette S; Peter S; Zhou W; Maguer-Satta V; Michallet M; Goldman J; Apperley JF; Mahon FO; Marin D; Etienne G

**INSTITUCIÓN / INSTITUTION:** - Centre Hospitalier Lyon Sud, Pierre Benite, France;

**RESUMEN / SUMMARY:** - The BCR-ABL T315I mutation confers resistance to currently licensed tyrosine kinase inhibitors in chronic myelogenous leukemia. However, the impact on survival at early stages of disease, in chronic phase, has never been detailed. Using matched pair analysis, a cohort of 64 chronic phase patients harboring a T315I mutation and resistant to imatinib mesylate, was compared to a similar cohort of 53 chronic phase patients resistant to imatinib, but with no detectable T315I mutation, in the pre-ponatinib era. These patients were matched according to age at diagnosis, interval between disease diagnosis and imatinib, imatinib duration. Kaplan-Meier survival analyses demonstrate the significant negative impact of the presence of the T315I mutation on overall (since imatinib-resistance T315I+ 48.4 months versus not reached for T315I-, p=0.006) and failure-free survival (since imatinib-resistance: T315I+ 34.7 months versus not reached for T315I-, p=0.003). In addition, Cox proportional hazard models adjusted on overall survival demonstrate the negative influence of the T315I mutation (p=0.02, HR=2.54). These results confirm early assumptions concerning the poor prognosis of chronic phase chronic myelogenous leukemia patients with the T315I mutation who are not

eligible for allogeneic transplant, and demonstrate the need for more therapeutic options.

[71]

**TÍTULO / TITLE:** - Colorectal cancer surgery in portal hypertensive patients: does adjuvant oxaliplatin affect prognosis?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dis Colon Rectum. 2013 May;56(5):577-85. doi: 10.1097/DCR.0b013e318286f8fc.

●●Enlace al texto completo (gratis o de pago)

[1097/DCR.0b013e318286f8fc](#)

**AUTORES / AUTHORS:** - Madbouly KM; Hussein AM; Zeid A

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**RESUMEN / SUMMARY:** - BACKGROUND: Oxaliplatin is used in adjuvant treatment of colorectal cancer and is associated with sinusoidal obstruction syndrome. Few data are available on its effects in patients in whom portal hypertension was diagnosed before cancer treatment. OBJECTIVE: Our aim was to investigate short- and long-term outcomes of surgery for colorectal cancer in patients with portal hypertension with or without cirrhosis, particularly regarding effects of adjuvant chemotherapy with oxaliplatin. DESIGN AND SETTING: This was a prospective cohort study performed at an academic medical center. PATIENTS: Patients with stage II or III colorectal cancer and portal hypertension who underwent curative resection were included. INTERVENTION: All patients received adjuvant chemotherapy with oxaliplatin (FOLFOX 4) or 5-fluorouracil and leucovorin. MAIN OUTCOME MEASURES: Potential predictive laboratory and clinical variables and postoperative (30-day) and long-term morbidity and mortality were recorded. RESULTS: Of 63 patients enrolled, 23 (37%) had a total of 82 postoperative complications; 5 patients (8%) died within 30 days postoperatively. Univariate analysis showed that severe portal hypertension, preoperative Child class B, low albumin, the presence of ascites, preoperative upper GI tract bleeding, and high intraoperative blood loss were linked to postoperative morbidity. Presence of postoperative infection ( $p = 0.004$ ), presence of preoperative ascites ( $p = 0.01$ ), high intraoperative blood loss ( $p = 0.02$ ), and preoperative upper GI tract bleeding ( $p = 0.03$ ) were significantly related to mortality. Of 58 patients receiving adjuvant chemotherapy, 20 received the oxaliplatin regimen and 38 received 5-fluorouracil/leucovorin without oxaliplatin. The median length of follow-up was 26 (range, 6-36) months. Kaplan-Meier analyses showed that patients who received oxaliplatin had higher cumulative incidences of newly developed esophageal varices ( $p = 0.002$ ), GI tract bleeding ( $p = 0.02$ ), and newly formed ascites ( $p = 0.03$ ). Death occurred in 8 of 20 patients (40%) in the oxaliplatin group and in 5 of 38 patients (13%) in the 5-fluorouracil group.

Kaplan-Meier estimates of mean survival time were 34.4 months (95% CI, 32.4-36.5) in the 5-fluorouracil/leucovorin group vs 29.9 months (95% CI, 26-33.7) in the oxaliplatin group, and patients receiving oxaliplatin had a significantly higher relative risk of death (HR = 2.98; 95% CI, 1.03-8.65). Cancer-specific mortality was not related to treatment type. LIMITATIONS: The study was limited by the relatively small sample size and lack of randomization, which may have led to selection bias in treatment regimens. CONCLUSIONS: Colorectal cancer surgery can be done safely in portal hypertensive patients with good hepatic function; however, higher mortality is expected in patients with compromised hepatic function reserve. Compared with adjuvant chemotherapy without oxaliplatin, oxaliplatin-based chemotherapy does not significantly reduce cancer-specific mortality and may increase overall morbidity and mortality. Therefore, oxaliplatin-based chemotherapy should be used with caution in patients who have portal hypertension, even in those with good liver function.

[72]

**TÍTULO / TITLE:** - REG1A Expression Status Suggests Chemosensitivity Among Advanced Thoracic Esophageal Squamous Cell Carcinoma Patients Treated with Esophagectomy Followed by Adjuvant Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 May 5.

●●Enlace al texto completo (gratis o de pago) [1245/s10434-013-2983-9](#)

**AUTORES / AUTHORS:** - Sato Y; Motoyama S; Nanjo H; Ito S; Yoshino K; Sasaki T; Kuribayashi K; Nagaki Y; Imai K; Saito H; Minamiya Y; Ogawa JI

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Akita University Graduate School of Medicine, Akita, 010-8543, Japan, [yusuke@doc.med.akita-u.ac.jp](mailto:yusuke@doc.med.akita-u.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: Regenerating gene 1A (REG1A) plays an important role in tissue regeneration and in cell proliferation in the mucous membrane of the gastrointestinal tract. We previously reported that the positive expression status of REG1A was predictive of chemoradiosensitivity in patients treated with preoperative chemoradiotherapy before esophagectomy or with definitive chemoradiotherapy. To further confirm the utility of REG1A as a chemosensitivity marker, we carried out an additional retrospective clinical study aimed at determining whether REG1A is a reliable chemosensitivity marker in patients treated with esophagectomy followed by adjuvant chemotherapy. METHOD: A total of 177 patients with T2-4 thoracic esophageal squamous cell carcinoma received curative surgery without preoperative treatment at Akita University Hospital between 2001 and 2011. A tissue microarray was constructed, and REG1A expression status was analyzed immunohistochemically. We then statistically analyzed the relationships between REG1A expression status and 5-year overall survival (OS), disease-

specific survival (DSS), and disease-free survival (DFS). RESULTS: In the adjuvant group (n = 105), REG1A-positive patients showed significantly better prognoses than REG1A-negative patients. (5-year OS, p = .0022; DSS, p = .0004; and DFS, p = .0040). However, there were no significant differences between REG1A-positive and REG1A-negative patients in the surgery group (n = 72). Univariate and multivariate analyses showed REG1A expression status to be a significant prognostic factor affecting 5-year DSS, comparable to lymph node metastatic status. CONCLUSION: The present study suggests REG1A expression status has the potential to be a highly reliable and clinically useful chemosensitivity marker in patients treated with advanced thoracic esophageal squamous cell carcinoma. REG1A expression status will provide a good indication of treatment strategy and enable more individualized treatment for patients.

[73]

**TÍTULO / TITLE:** - Prognostic Score Including Gene Mutations in Chronic Myelomonocytic Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 20.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.47.3314](https://doi.org/10.1200/JCO.2012.47.3314)

**AUTORES / AUTHORS:** - Itzykson R; Kosmider O; Renneville A; Gelsi-Boyer V; Meggendorfer M; Morabito M; Berthon C; Ades L; Fenau P; Beyne-Rauzy O; Vey N; Braun T; Haferlach T; Dreyfus F; Cross NC; Preudhomme C; Bernard OA; Fontenay M; Vainchenker W; Schnittger S; Birnbaum D; Droin N; Solary E

**INSTITUCIÓN / INSTITUTION:** - Raphael Itzykson, Margot Morabito, Olivier A. Bernard, William Vainchenker, Nathalie Droin, Eric Solary, Institut Gustave Roussy, Villejuif; Raphael Itzykson, Margot Morabito, William Vainchenker, Nathalie Droin, Eric Solary, Université Paris-Sud, Le Kremlin-Bicêtre, Orsay; Olivier Kosmider, François Dreyfus, Michaela Fontenay, Assistance Publique-Hopitaux de Paris, Hôpital Cochin; Olivier Kosmider, François Dreyfus, Michaela Fontenay, Université Paris Descartes; Olivier Kosmider, Michaela Fontenay, Institut Cochin, Paris; Aline Renneville, Céline Berthon, Claude Preudhomme, Centre Hospitalier Régional Universitaire of Lille; Aline Renneville, Céline Berthon, Claude Preudhomme, University of Lille Nord de France; Aline Renneville, Claude Preudhomme, Inserm, Cancer Research Institute of Lille, Lille; Veronique Gelsi-Boyer, Norbert Vey, Daniel Birnbaum, Institut Paoli-Calmettes, Marseille; Lionel Ades, Pierre Fenau, Thorsten Braun, Hôpital Avicenne, Assistance Publique-Hopitaux de Paris, University Paris XIII, Bobigny; Odile Beyne-Rauzy, Centre Hospitalier Régional Universitaire de Toulouse, Toulouse, France; Manja Meggendorfer, Thorsten Haferlach, Susanne Schnittger, Munich Leukemia Laboratory, Munich, Germany; Nicholas C.P. Cross, University of Southampton; Nicholas C.P. Cross, Wessex Regional Genetics Laboratory, Salisbury, United Kingdom.

**RESUMEN / SUMMARY:** - PURPOSE Several prognostic scoring systems have been proposed for chronic myelomonocytic leukemia (CMML), a disease in which some gene mutations-including ASXL1-have been associated with poor prognosis in univariable analyses. We developed and validated a prognostic score for overall survival (OS) based on mutational status and standard clinical variables. PATIENTS AND METHODS We genotyped ASXL1 and up to 18 other genes including epigenetic (TET2, EZH2, IDH1, IDH2, DNMT3A), splicing (SF3B1, SRSF2, ZRSF2, U2AF1), transcription (RUNX1, NPM1, TP53), and signaling (NRAS, KRAS, CBL, JAK2, FLT3) regulators in 312 patients with CMML. Genotypes and clinical variables were included in a multivariable Cox model of OS validated by bootstrapping. A scoring system was developed using regression coefficients from this model. Results ASXL1 mutations (P < .0001) and, to a lesser extent, SRSF2 (P = .03), CBL (P = .003), and IDH2 (P = .03) mutations predicted inferior OS in univariable analysis. The retained independent prognostic factors included ASXL1 mutations, age older than 65 years, WBC count greater than 15 x10<sup>9</sup>/L, platelet count less than 100 x10<sup>9</sup>/L, and anemia (hemoglobin < 10 g/dL in female patients, < 11g/dL in male patients). The resulting five-parameter prognostic score delineated three groups of patients with median OS not reached, 38.5 months, and 14.4 months, respectively (P < .0001), and was validated in an independent cohort of 165 patients (P < .0001). CONCLUSION A new prognostic score including ASXL1 status, age, hemoglobin, WBC, and platelet counts defines three groups of CMML patients with distinct outcomes. Based on concordance analysis, this score appears more discriminative than those based solely on clinical parameters.

[74]

**TÍTULO / TITLE:** - Correction for Sievert et al., Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proc Natl Acad Sci U S A. 2013 May 21;110(21):8750. doi: 10.1073/pnas.1307863110. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1073/pnas.1307863110](https://doi.org/10.1073/pnas.1307863110)

[75]

**TÍTULO / TITLE:** - Nab-paclitaxel for first-line treatment of patients with metastatic breast cancer and poor prognostic factors: a retrospective analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Apr;138(3):829-37. doi: 10.1007/s10549-013-2447-8. Epub 2013 Apr 6.

●●Enlace al texto completo (gratuito o de pago) [1007/s10549-013-2447-](https://doi.org/10.1007/s10549-013-2447-8)

[8](#)

**AUTORES / AUTHORS:** - O'Shaughnessy J; Gradishar WJ; Bhar P; Iglesias J

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**RESUMEN / SUMMARY:** - Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has demonstrated clinical benefit in metastatic breast cancer (MBC) in a randomized phase III trial versus paclitaxel (CA012; N = 454) and in a randomized phase II trial versus docetaxel (CA024; N = 300). This retrospective analysis examines whether patients with poor prognostic factors demonstrate similar outcomes to the intent-to-treat (ITT) populations in these trials. This retrospective analysis evaluated the efficacy and safety of previously untreated patients with MBC with the following poor prognostic factors: visceral dominant metastases and short disease-free interval (DFI;  $\leq 2$  years). In CA012 (n = 186 first-line patients), nab-paclitaxel demonstrated a significantly higher overall response rate (ORR) versus paclitaxel in patients with visceral dominant metastases (42 vs. 23 %; P = 0.022), whereas the higher ORR for nab-paclitaxel in patients with a short DFI (43 vs. 33 %; P = NS) was not statistically significant. In CA024, a significantly higher ORR for nab-paclitaxel 150 mg/m<sup>2</sup> versus docetaxel was observed in patients with visceral dominant metastases (76 vs. 37 %; P < 0.001). No significant differences in ORR were observed in patients with a short DFI. Although progression-free survival (PFS) and overall survival showed trends similar to ORR, statistical significance was only achieved for comparisons of PFS in patients with visceral dominant metastases in CA024 (13.1 months for nab-paclitaxel 150 mg/m<sup>2</sup> vs. 7.8 months for docetaxel [P = 0.019] and 7.5 months for nab-paclitaxel 100 mg/m<sup>2</sup> [P = 0.010]). Safety results were similar to previous reports of the ITT populations. nab-Paclitaxel demonstrated similar efficacy in patients with poor prognostic factors as in the ITT populations of these two trials. In each trial, ORR was significantly higher for nab-paclitaxel versus the comparator taxane among patients with visceral dominant metastases.

[76]

**TÍTULO / TITLE:** - In vitro and in vivo effects of phenethyl isothiocyanate treatment on vimentin protein expression in cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65 Suppl 1:61-7. doi: 10.1080/01635581.2013.785002.

●●Enlace al texto completo (gratuito o de pago)

[1080/01635581.2013.785002](https://doi.org/10.1080/01635581.2013.785002)

**AUTORES / AUTHORS:** - Sakao K; Hahm ER; Singh SV

**INSTITUCIÓN / INSTITUTION:** - a Department of Pharmacology & Chemical Biology , University of Pittsburgh Cancer Institute.

**RESUMEN / SUMMARY:** - We have shown previously that cancer prevention by cruciferous vegetable constituent phenethyl isothiocyanate (PEITC) in a transgenic mouse model of prostate cancer is associated with induction of E-cadherin protein expression. Because suppression of E-cadherin protein concomitant with induction of mesenchymal markers (e.g., vimentin) is a biochemical hallmark of epithelial-mesenchymal transition, a process implicated in cancer metastasis, we hypothesized that PEITC treatment was likely to suppress vimentin protein expression. Contrary to this prediction, exposure of human breast (MDA-MB-231) and prostate cancer cells (PC-3 and DU145) to PEITC resulted in a dose-dependent increase in vimentin protein level, which was observed as early as 6 h posttreatment and persisted for the duration of the experiment (24 h). RNA interference of vimentin resulted in a modest augmentation of PEITC-mediated inhibition of MDA-MB-231 and PC-3 cell migration as well as cell viability. Furthermore, the PEITC-induced apoptosis was moderately increased upon siRNA knockdown of vimentin protein in MDA-MB-231 and PC-3 cells. To our surprise, PEITC treatment caused a marked decrease in vimentin protein expression in breast and prostate carcinoma in vivo in transgenic mouse models, although the difference was statistically significant only in the breast carcinomas. The present study highlights the importance of in vivo correlative studies for validation of the in vitro mechanistic observations.

[77]

**TÍTULO / TITLE:** - A prognostic model predicts the risk of distant metastasis and death for patients with nasopharyngeal carcinoma based on pre-treatment serum C-reactive protein and N-classification.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Apr 6. pii: S0959-8049(13)00188-3. doi: 10.1016/j.ejca.2013.03.003.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.03.003](#)

**AUTORES / AUTHORS:** - Xia WX; Zhang HB; Shi JL; Lu X; Wang L; Ye YF; Cao KJ; Qian CN; Guo X; Xiang YQ

**INSTITUCIÓN / INSTITUTION:** - Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, Guangzhou 510060, PR China; State Key Laboratory of Oncology in Southern China, Guangzhou 510060, PR China.

**RESUMEN / SUMMARY:** - **PURPOSE:** Chronic inflammation plays an important role in nasopharyngeal carcinoma (NPC) development and progression. Aim of this study is to determine whether inflammation-related parameters predict distant metastasis in NPC patients. **MATERIALS AND METHODS:** 335 newly diagnosed non-metastatic NPC patients were recruited. The values of the C-reactive protein (CRP), lactate dehydrogenase, albumin, globulin, white blood

cell and neutrophil at baseline were measured. RESULTS: Among the above six parameters, only CRP was independently associated with distant metastasis-free survival (DMFS). CRP concentration of advanced T-/TNM-classification patients was higher than those with early classification (P=0.001). Higher-CRP (CRP≥2.46mg/L) predicted shorter overall survival, disease-free survival and DMFS than lower-CRP (CRP<2.46mg/L). In a multivariable model, higher-CRP and advanced N-classification were independent predictors of distant metastasis. On the basis of these two parameters, a prognostic NC-model was developed as following: (1) low-risk (early N-classification and lower-CRP); (2) intermediate-risk (advanced N-classification or higher-CRP) and (3) the high-risk distant metastasis (advanced N-classification and higher-CRP). When compared with the low-risk group, the hazard ratios (HRs) for distant metastasis and death for the intermediate-/high-risk patients were 3.6/16.1 and 2.26/7.61, respectively (both P<0.001). CONCLUSION: We developed a new prognostic model based on CRP and N-classification for predicting distant metastasis and death of NPC patients, which may facilitate patient counselling and individualised treatment.

[78]

**TÍTULO / TITLE:** - Genetic polymorphisms of enzymes related to oral tegafur/uracil therapeutic efficacy in patients with hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Jul;24(6):617-22. doi: 10.1097/CAD.0b013e3283614fef.

●●Enlace al texto completo (gratis o de pago)

[1097/CAD.0b013e3283614fef](#)

**AUTORES / AUTHORS:** - Fushiya N; Takagi I; Nishino H; Akizuki S; Ohnishi A

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Internal Medicine, Division of Gastroenterology and Hepatology bDepartment of Laboratory Medicine, Daisan Hospital, The Jikei University School of Medicine, Tokyo, Japan.

**RESUMEN / SUMMARY:** - Oral tegafur/uracil therapy has been indicated for patients with hepatocellular carcinoma (HCC) and is often used as a single-agent treatment. However, how the treatment efficacy is related to 5-fluorouracil (5-FU) metabolic enzymes is unclear. We investigated genetic polymorphisms of the 5-FU metabolic enzymes in Japanese patients with HCC. We examined two genetic polymorphisms of the metabolic enzymes cytochrome P450 2A6 (CYP2A6) and dihydropyrimidine dehydrogenase (DPD) in 58 Japanese hepatitis C virus-seropositive HCC patients. To measure efficacy, we investigated genetic polymorphisms of the variable number of tandem repeats (VNTRs) of thymidylate synthase (TS) and classified the genotypes as high or low expression types. The frequency of the CYP2A6\*4 allele (no-activity allele) among 58 HCC patients was 0.233 and a homozygous genotype (\*4/\*4) was found in five patients. The heterozygous genotype (T/C) of DPYD\*9 (T85C) was

detected in eight patients and the frequency of the DPYD\*9 allele among 58 HCC patients was 0.069. Of 58 patients, 42 were classified as high expression type and 16 as low expression type for TS VNTR. Fifteen of these 16 patients appeared to have normal CYP2A6 metabolic activity and 13 of these 15 patients likely had normal DPD metabolic activity. Only 13 of 58 HCC patients (22.4%) tested may respond positively to treatment with oral tegafur/uracil. Therefore, when administering oral 5-FU in patients with HCC, it is important to consider three genetic polymorphisms (CYP2A6, DPYD, and TS) associated with 5-FU metabolic enzymes.

[79]

**TÍTULO / TITLE:** - Gefitinib in non-small cell lung carcinoma: a case report of an unusual side effect and complete response in advanced disease.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumori. 2013 Jan-Feb;99(1):3e-5e. doi:

10.1700/1248.13802.

●●Enlace al texto completo (gratis o de pago) [1700/1248.13802](#)

**AUTORES / AUTHORS:** - Laterza MM; Chiurazzi B; Brangi M; Riccardi F; Carteni G

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology Studies, Second University of Naples, Naples, Italy. [marilena\\_laterza@yahoo.it](mailto:marilena_laterza@yahoo.it)

**RESUMEN / SUMMARY:** - Gefitinib is a tyrosine kinase inhibitor, indicated in advanced non-small cell lung cancer in all lines of treatment for patients harboring EGFR mutations. It has a favorable toxicity profile but may induce unexpected adverse effects, such as an inflammatory reaction in the bladder. We report a rare case of hemorrhagic cystitis, an unusual side effect, in a patient with non-small cell lung cancer treated with gefitinib, which did not compromise the clinical response.

[80]

**TÍTULO / TITLE:** - Diagnosis, prognosis and treatment of patients with gastrointestinal stromal tumour (GIST) and germline mutation of KIT exon 13.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 May 3. pii: S0959-8049(13)00307-9. doi: 10.1016/j.ejca.2013.04.005.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.04.005](#)

**AUTORES / AUTHORS:** - Bachet JB; Landi B; Laurent-Puig P; Italiano A; Le Cesne A; Levy P; Safar V; Duffaud F; Blay JY; Emile JF

**INSTITUCIÓN / INSTITUTION:** - EA4340 'Epidemiologie et Oncogenese des tumeurs digestives', Versailles Saint-Quentin-en-Yvelines University, 78280 Guyancourt, France; Hepato-Gastroenterology Department, Pitie Salpetriere

Hospital, 75013 Paris, France; Medical University Pierre et Marie Curie, UFR Paris VI, France.

**RESUMEN / SUMMARY:** - BACKGROUND: The demonstration of the role of activating mutations of KIT or PDGFRA and the development of targeted therapies have modified the prognosis of patients with gastrointestinal stromal tumours (GISTs). Identification of kindreds with KIT or PDGFRA germline mutation raised new questions, especially regarding the diagnosis, management, monitoring and treatment of these patients. METHODS: We identified index patients of three different families with a KIT exon 13 germline mutation. Pedigree of GIST kindred was assessed in oncogenetic consultation, and medical records were reviewed. Efficacy of imatinib in GISTs with KIT exon 13 was evaluated and compared with published data. RESULTS: All KIT germline mutations were p.K642E. Twenty affected patients were identified in the three families. GISTs were multiple and occurred before 45years in all but one case. All resected tumours were of spindle cell histology, CD117 positive, and had low or intermediate risk of relapse. Lentiginos involving the palms and soles were detected in four patients, and three patients had motrice dysphagia. Nine affected patients died of their disease, all but one before 65years. Affected patients were most often symptomatic and required iterative surgical resections. Imatinib was efficient in GISTs with p.K642E mutation with a disease control rate superior to 90% whatever the sporadic or inherited origin of the tumour. CONCLUSIONS: We propose a regular screening of kindreds who have germline mutation. Treatment with imatinib should be considered for those with symptomatic tumour, larger than 3cm and/or growing rapidly.

[81]

**TÍTULO / TITLE:** - Genomic instability may originate from imatinib-refractory chronic myeloid leukemia stem cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 16;121(20):4175-83. doi: 10.1182/blood-2012-11-466938. Epub 2013 Mar 29.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2012-11-466938](#)

**AUTORES / AUTHORS:** - Bolton-Gillespie E; Schemionek M; Klein HU; Flis S; Hoser G; Lange T; Nieborowska-Skorska M; Maier J; Kerstiens L; Koptyra M; Muller MC; Modi H; Stoklosa T; Seferynska I; Bhatia R; Holyoake TL; Koschmieder S; Skorski T

**INSTITUCIÓN / INSTITUTION:** - Department of Microbiology and Immunology, School of Medicine, Temple University, Philadelphia, PA;

**RESUMEN / SUMMARY:** - Genomic instability is a hallmark of chronic myeloid leukemia in chronic phase (CML-CP) resulting in BCR-ABL1 mutations encoding resistance to tyrosine kinase inhibitors (TKIs) and/or additional chromosomal aberrations leading to disease relapse and/or malignant

progression. TKI-naive and TKI-treated leukemia stem cells (LSCs) and leukemia progenitor cells (LPCs) accumulate high levels of reactive oxygen species (ROS) and oxidative DNA damage. To determine the role of TKI-refractory LSCs in genomic instability, we used a murine model of CML-CP where ROS-induced oxidative DNA damage was elevated in LSCs, including quiescent LSCs, but not in LPCs. ROS-induced oxidative DNA damage in LSCs caused clinically relevant genomic instability in CML-CP-like mice, such as TKI-resistant BCR-ABL1 mutations (E255K, T315I, H396P), deletions in *Ikzf1* and *Trp53*, and additions in *Zfp423* and *Idh1*. Despite inhibition of BCR-ABL1 kinase, imatinib did not downregulate ROS and oxidative DNA damage in TKI-refractory LSCs to the levels detected in normal cells, and CML-CP-like mice treated with imatinib continued to accumulate clinically relevant genetic aberrations. Inhibition of class I p21-activated protein kinases by IPA3 downregulated ROS in TKI-naive and TKI-treated LSCs. Altogether, we postulate that genomic instability may originate in the most primitive TKI-refractory LSCs in TKI-naive and TKI-treated patients.

[82]

**TÍTULO / TITLE:** - Does histology predict survival of advanced non-small cell lung cancer patients treated with platin-based chemotherapy? An analysis of the Eastern Cooperative Oncology Group Study E1594.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Apr 20. pii: S0169-5002(13)00123-2. doi: 10.1016/j.lungcan.2013.03.018.

●●Enlace al texto completo (gratis o de pago)

[1016/j.lungcan.2013.03.018](#)

**AUTORES / AUTHORS:** - Hoang T; Dahlberg SE; Schiller JH; Johnson DH

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[txh@medicine.wisc.edu](mailto:txh@medicine.wisc.edu).

**RESUMEN / SUMMARY:** - INTRODUCTION: We conducted this analysis to determine whether survival of advanced NSCLC patients treated with platin-based chemotherapy doublets involving paclitaxel, docetaxel or gemcitabine was dependent on histological subtypes and treatment regimen. METHODS: We retrospectively analyzed data from E1594, a front-line phase III study in which advanced NSCLC patients were randomized to receive one of four regimens: cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, and carboplatin-paclitaxel. Patients were classified into four histology groups: squamous cell (SCC), adeno- (AC), large cell (LCC) and others including not otherwise specified (O/NOS) carcinoma. Logrank test was performed to compare overall survival (OS) and progression free survival (PFS) distributions according to histology as well as treatment. RESULTS: Of 1139 patients

including 716 men and 423 women, AC was the most common subtype (56.8%), followed by SCC (19.7%), O/NOS (17.0%) and LCC (6.5%). Men were more likely to have SCC and women were more likely to have AC (p=0.002). Among the four histology groups, there was no imbalance in regard to race, performance status, weight loss, brain metastasis or treatment. In each histology group, we found no significant difference in OS and PFS between the four chemotherapy regimens. Conversely, in each treatment arm, the survival outcome was similar between the four histology subtypes. CONCLUSIONS: Our analysis suggests that histology does not predict survival benefit in advanced NSCLC patients treated with first-line platin-based doublets involving paclitaxel, docetaxel or gemcitabine.

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[83]

**TÍTULO / TITLE:** - Characteristics of pharmacogenomics/biomarker-guided clinical trials for regulatory approval of anti-cancer drugs in Japan.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hum Genet. 2013 May 9. doi: 10.1038/jhg.2013.36.

●●Enlace al texto completo (gratis o de pago) [1038/jhg.2013.36](#)

**AUTORES / AUTHORS:** - Ishiguro A; Yagi S; Uyama Y

**INSTITUCIÓN / INSTITUTION:** - Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan.

**RESUMEN / SUMMARY:** - Pharmacogenomics (PGx) or biomarker (BM) has the potential to facilitate the development of safer and more effective drugs in terms of their benefit/risk profiles by stratifying population into categories such as responders/non-responders and high-/low-risks to drug-induced serious adverse reactions. In the past decade, practical use of PGx or BM has advanced the field of anti-cancer drug development. To identify the characteristics of the PGx/BM-guided clinical trials for regulatory approval of anti-cancer drugs in Japan, we collected information on design features of 'key trials' in the review reports of anti-cancer drugs that were approved after the implementation of the 'Revised Guideline for the Clinical Evaluation of Anti-cancer drugs' in April 2006. On the basis of the information available on the regulatory review data for the newly approved anti-cancer drugs in Japan, this article aims to explain the limitations and points to consider in the study design of PGx/BM-guided clinical trials. Journal of Human Genetics advance online publication, 9 May 2013; doi:10.1038/jhg.2013.36.

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[84]

**TÍTULO / TITLE:** - c-Src modulates estrogen-induced stress and apoptosis in estrogen-deprived breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-4152](https://doi.org/10.1158/0008-5472.CAN-12-4152)

**AUTORES / AUTHORS:** - Fan P; Griffith OL; Agboke F; Anur P; Zou X; McDaniel RE; Creswell K; Kim SH; Katzenellenbogen JA; Gray JW; Jordan VC Obe

**INSTITUCIÓN / INSTITUTION:** - Oncology, Georgetown University.

**RESUMEN / SUMMARY:** - The emergence of antiestrogen resistance in breast cancer is an important clinical phenomenon affecting long-term survival in this disease. Identifying factors that convey cell survival in this setting may guide improvements in treatment. Estrogen (E2) can induce apoptosis in breast cancer cells that have been selected for survival after E2 deprivation for long periods (MCF-7:5C cells), but the mechanisms underlying E2-induced stress in this setting have not been elucidated. Here, we report that the c-Src kinase functions as a key adapter protein for the estrogen receptor (ER, ESR1) in its activation of stress responses induced by E2 in MCF-7:5C cells. E2 elevated phosphorylation of c-Src which was blocked by 4-hydroxytamoxifen (4-OHT), suggesting that E2 activated c-Src through the ER. We found that E2 activated the sensors of the unfolded protein response (UPR), IRE1alpha (ERN1) and PERK kinase (EIF2AK3), the latter of which phosphorylates eukaryotic translation initiation factor-2alpha (eIF2alpha). E2 also dramatically increased reactive oxygen species (ROS) production and up-regulated expression of heme oxygenase HO-1 (HMOX1), an indicator of oxidative stress, along with the central energy sensor kinase AMPK (PRKAA2). Pharmacological or RNAi-mediated inhibition of c-Src abolished the phosphorylation of eIF2alpha and AMPK, blocked E2-induced ROS production, and inhibited E2-induced apoptosis. Together, our results establish that c-Src kinase mediates stresses generated by E2 in long-term E2-deprived cells that trigger apoptosis. This work offers a mechanistic rationale for a new approach in the treatment of endocrine-resistant breast cancer.

[85]

**TÍTULO / TITLE:** - Prediction of response to neoadjuvant chemotherapy in breast cancer patients by circulating apoptotic biomarkers nucleosomes, DNase, cytokeratin-18 fragments and survivin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Apr 21. pii: S0304-3835(13)00347-9. doi: 10.1016/j.canlet.2013.04.013.

●●Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.04.013](https://doi.org/10.1016/j.canlet.2013.04.013)

**AUTORES / AUTHORS:** - Stoetzer OJ; Fersching DM; Salat C; Steinkohl O; Gabka CJ; Hamann U; Braun M; Feller AM; Heinemann V; Siegele B; Nagel D; Holdenrieder S

**INSTITUCIÓN / INSTITUTION:** - Haematology and Oncology Outpatient Cancer Care Center, Franz-Schrank-Str. 2, 80638 Munich, Germany.

**RESUMEN / SUMMARY:** - Biomarkers predicting response to neoadjuvant chemotherapy in locally confined breast cancer (LBC) are highly needed. We prospectively assessed serial blood levels of apoptotic biomarkers nucleosomes, DNase activity, cytokeratin-18 fragments (M30) and survivin in 51 LBC patients and correlated them with response to neoadjuvant treatment and established tumor markers. As controls, we used 31 healthy subjects, 13 patients with benign diseases and 28 with metastatic breast cancer (MBC). Levels of nucleosomes and survivin were elevated in LBC and MBC while M30, CEA and CA 15-3 levels were only elevated in MBC. During neoadjuvant chemotherapy, LBC patients with no change of disease (N=13) had significantly higher pretherapeutic levels of nucleosomes than patients with remission (N=38). We conclude that apoptotic biomarkers bear valuable information for diagnosis and therapy response prediction in LBC patients.

[86]

**TÍTULO / TITLE:** - A randomized, multi-center, open-label, phase II study of once-per-cycle DA-3031, a biosimilar pegylated G-CSF, compared with daily filgrastim in patients receiving TAC chemotherapy for early-stage breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Invest New Drugs. 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1007/s10637-013-9973-](#)

[4](#)

**AUTORES / AUTHORS:** - Park KH; Sohn JH; Lee S; Park JH; Kang SY; Kim HY; Park IH; Park YH; Im YH; Lee HJ; Hong DS; Park S; Shin SH; Kwon HC; Seo JH

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology/Hematology, Department of Internal medicine, Korea University College of Medicine, 97 Guro-dong Gil, Guro-gu, Seoul, Korea.

**RESUMEN / SUMMARY:** - Backgrounds A pegylated form of recombinant granulocyte-colony stimulating factor (G-CSF) was developed for prophylactic use in breast cancer. The aim of this study was to evaluate the efficacy and safety of once-per-cycle DA-3031 in patients receiving chemotherapy for breast cancer. Methods A total of 61 patients receiving docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy were randomized in cycle 1 to receive daily injections of filgrastim (100 mug/m<sup>2</sup>) or a single subcutaneous injection of pegylated filgrastim DA-3031 at a dose of either 3.6 mg or 6 mg. Results The mean duration of grade 4 neutropenia in cycle 1 was comparable among the treatment groups (2.48, 2.20, and 2.05 days for filgrastim, DA-3031 3.6 mg and 6 mg, respectively; P = 0.275). No statistically significant differences were observed in the incidence of febrile neutropenia between the treatment groups (9.5 %, 15.0 %, and 5.0 % for filgrastim, DA-3031 3.6 mg and 6 mg, respectively; P = 0.681) in cycle 1. The incidences of adverse events attributable to G-CSF were similar among the treatment groups. Conclusions

Fixed doses of 3.6 mg or 6 mg DA-3031 have an efficacy comparable to that of daily injections of filgrastim in ameliorating grade 4 neutropenia in patients receiving TAC chemotherapy.

[87]

**TÍTULO / TITLE:** - Elevated level of peripheral CD8(+)CD28 (-) T lymphocytes are an independent predictor of progression-free survival in patients with metastatic breast cancer during the course of chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Immunol Immunother. 2013 Jun;62(6):1123-30. doi: 10.1007/s00262-013-1424-8. Epub 2013 Apr 21.

●●Enlace al texto completo (gratis o de pago) [1007/s00262-013-1424-](#)

[8](#)

**AUTORES / AUTHORS:** - Song G; Wang X; Jia J; Yuan Y; Wan F; Zhou X; Yang H; Ren J; Gu J; Lyerly HK

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, 52 Fucheng Rd, Beijing, 100142, China.

**RESUMEN / SUMMARY:** - PURPOSE: Suppression of cellular immunity resulting from tumorigenesis and/or therapy might promote cancer cells' growth, progression and invasion. Here, we explored whether T lymphocyte subtypes from peripheral blood of metastatic breast cancer (MBC) female patients could be used as alternative surrogate markers for cancer progress. Additionally, plasma levels of interleukin (IL)-2, IL-4, IL-6, IL-10, IFN-gamma, and transforming growth factor-beta1 were quantitated from MBC and healthy volunteers. EXPERIMENTAL DESIGN: This study included 89 female MBC patients during the post-salvage chemotherapy follow-up and 50 age- and sex-matched healthy volunteers as control. The percentages of T lymphocyte subpopulations from peripheral blood and plasma levels of cytokines were measured. RESULTS: Both CD8(+)CD28(-) and CD4(+)CD25(+) were elevated in MBC patients compared to the control cohort (P < 0.05). In contrast, CD3(+) and CD8(+)CD28(+) cells were significantly lower in MBC patients (P < 0.0001, P = 0.045, respectively). MBC patients had elevated levels of immunosuppressive cytokines IL-6 and IL-10. Patients with elevated CD8(+)CD28(-) and CD4(+)CD25(+) cells showed increased levels of IL-6, and only patients with elevated CD8(+)CD28(-) had decreased interferon-gamma. Univariate analysis indicated increased CD3(+)CD4(+) or CD8(+)CD28(+) correlated with prolonged progression-free survival (PFS), while elevated CD8(+)CD28(-) associated with shorten PFS. The percent of CD8(+)CD28(-) T lymphocytes is an independent predictor for PFS through multivariate analysis. CONCLUSIONS: This study suggests that progressive

elevated levels of CD8(+)/CD28(-) suppressor T lymphocytes represent a novel independent predictor of PFS during post-chemotherapy follow-up.

[88]

**TÍTULO / TITLE:** - Gene expression profiling identifies EPHB4 as a potential predictive biomarker in colorectal cancer patients treated with bevacizumab.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):572. doi: 10.1007/s12032-013-0572-1. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0572-](#)

[1](#)

**AUTORES / AUTHORS:** - Guijarro-Munoz I; Sanchez A; Martinez-Martinez E; Garcia JM; Salas C; Provencio M; Alvarez-Vallina L; Sanz L

**INSTITUCIÓN / INSTITUTION:** - Molecular Immunology Unit, Hospital Universitario Puerta de Hierro Majadahonda, Joaquin Rodrigo 2, 28222 Madrid, España.

**RESUMEN / SUMMARY:** - The anti-VEGF monoclonal antibody bevacizumab was approved in 2004 as a first-line treatment for metastatic colorectal cancer (CRC) in combination with chemotherapy and provided proof of principle for antiangiogenic therapy. However, there is no biomarker that can help to select patients who may benefit from bevacizumab in order to improve cost-effectiveness and therapeutic outcomes. The aim of this study was to compare gene expression profiles in CRC patients treated with bevacizumab who responded to the treatment with those that did not respond, in an effort to identify potential predictive biomarkers. RNA isolated from formalin-fixed paraffin-embedded tumor specimens of patients treated with bevacizumab was subjected to gene expression analysis with quantitative RT-PCR arrays profiling 84 genes implicated in the angiogenic process. Data were validated at the protein level using immunohistochemistry. We identified a gene, EPHB4, whose expression was significantly increased in nonresponders ( $p = 0.048$ , Mann-Whitney test). Furthermore, high EPHB4 tumor levels were associated with decreased median overall survival (16 months vs 48, Log-rank  $p = 0.012$ ). This was not observed in a control group of CRC patients treated only with chemotherapy, suggesting that EPHB4 constitutes a potential predictive biomarker and not a mere prognostic one. These data support the notion of a potential synergy between EPHB4-EFNB2 and VEGF-VEGFR pathways, making patients with high EPHB4 expression more resistant to VEGF blocking. Therefore, determination of EPHB4 levels in CRC samples could be useful for the prediction of response to bevacizumab.

[89]

**TÍTULO / TITLE:** - Impact of EGFR Inhibitor in Non-Small Cell Lung Cancer on Progression-Free and Overall Survival: A Meta-Analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Natl Cancer Inst. 2013 May 1;105(9):595-605. doi: 10.1093/jnci/djt072. Epub 2013 Apr 17.

●●Enlace al texto completo (gratis o de pago) [1093/jnci/djt072](#)

**AUTORES / AUTHORS:** - Lee CK; Brown C; Gralla RJ; Hirsh V; Thongprasert S; Tsai CM; Tan EH; Ho JC; Chu da T; Zaatar A; Osorio Sanchez JA; Vu VV; Au JS; Inoue A; Lee SM; GebSKI V; Yang JC

**INSTITUCIÓN / INSTITUTION:** - Graduate Institute of Oncology and Cancer Research Center, National Taiwan University College of Medicine, Taipei 10051, Taiwan. [chihyang@ntu.edu.tw](mailto:chihyang@ntu.edu.tw).

**RESUMEN / SUMMARY:** - Background The epidermal growth factor receptor (EGFR) signaling pathway is crucial for regulating tumorigenesis and cell survival and may be important in the development and progression of non-small cell lung cancer (NSCLC). We examined the impact of EGFR-tyrosine kinase inhibitors (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations. Methods Randomized trials that compared EGFR-TKIs monotherapy or combination EGFR-TKIs-chemotherapy with chemotherapy or placebo were included. We used published hazard ratios (HRs), if available, or derived treatment estimates from other survival data. Pooled estimates of treatment efficacy of EGFR-TKIs for the EGFR mutation-positive (EGFRmut(+)) and EGFR mutation-negative (EGFRmut(-)) subgroups were calculated with the fixed-effects inverse variance weighted method. All statistical tests were two-sided. Results We included 23 eligible trials (13 front-line, 7 second-line, 3 maintenance; n = 14570). EGFR mutation status was known in 31% of patients. EGFR-TKIs treatment prolonged PFS in EGFRmut(+) patients, and EGFR mutation was predictive of PFS in all settings: The front-line hazard ratio for EGFRmut(+) was 0.43 (95% confidence interval [CI] = 0.38 to 0.49; P < .001), and the front-line hazard ratio for EGFRmut(-) was 1.06 (95% CI = 0.94 to 1.19; P = .35; P interaction < .001). The second-line hazard ratio for EGFRmut(+) was 0.34 (95% CI = 0.20 to 0.60; P < .001), and the second-line hazard ratio for EGFRmut(-) was 1.23 (95% CI = 1.05 to 1.46; P = .01; P interaction < .001). The maintenance hazard ratio for EGFRmut(+) was 0.15 (95% CI = 0.08 to 0.27; P < .001), and the maintenance hazard ratio for EGFRmut(-) was 0.81 (95% CI = 0.68 to 0.97; P = .02; P interaction < .001). EGFR-TKIs treatment had no impact on OS for EGFRmut(+) and EGFRmut(-) patients. Conclusions EGFR-TKIs therapy statistically significantly delays disease progression in EGFRmut(+) patients but has no demonstrable impact on OS. EGFR mutation is a predictive biomarker of PFS benefit with EGFR-TKIs treatment in all settings. These findings support EGFR mutation assessment before initiation of treatment. EGFR-TKIs should be considered as front-line therapy in EGFRmut(+) advanced NSCLC patients.

[90]

**TÍTULO / TITLE:** - Gas6/Axl mediates tumor cell apoptosis, migration and invasion and predicts the clinical outcome of osteosarcoma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 15. pii: S0006-291X(13)00789-4. doi: 10.1016/j.bbrc.2013.05.019.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.019](http://1016/j.bbrc.2013.05.019)

**AUTORES / AUTHORS:** - Han J; Tian R; Yong B; Luo C; Tan P; Shen J; Peng T

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**RESUMEN / SUMMARY:** - Dysregulation of the receptor tyrosine kinase Axl and its ligand Gas6 has been shown to promote multiple tumorigenic processes, as well as to correlate with worse prognosis in many different tumor types. However, studies of Axl expression and function in osteosarcoma have rarely been reported. In this study, we report that activated Axl is highly expressed in osteosarcoma cells, and this expression is significantly correlated with the recurrence and lung metastasis of osteosarcoma patients. High expression of activated Axl was an independent predictor for worse prognosis in osteosarcoma. Additionally, we confirmed a strong positive correlation between P-Axl and MMP-9 expression in those osteosarcoma patients. In osteosarcoma cell lines MG63 and U2OS, 200ng/ml rhGas6 could cause obvious increase of P-Axl expression within 30min, consistent with the expression of P-AKT. In both of the cell lines, Axl activated by rhGas6 could protect the tumor cells from apoptosis caused by serum starvation, and promote tumor cells' migration and invasion in vitro. Together with previous data, these studies suggest that activated Axl participate in the progression of osteosarcoma by resisting tumor cells apoptosis and promoting their migration and invasion, which may be linked to the expression of MMP-9. In the mechanism, AKT signaling pathway may contribute to the function of P-Axl in osteosarcoma rather than ERK pathway.

[91]

**TÍTULO / TITLE:** - Use of beta-Blockers, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Risk of Breast Cancer Recurrence: A Danish Nationwide Prospective Cohort Study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 6.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.43.9190](http://1200/JCO.2012.43.9190)

**AUTORES / AUTHORS:** - Sorensen GV; Ganz PA; Cole SW; Pedersen LA; Sorensen HT; Cronin-Fenton DP; Garne JP; Christiansen PM; Lash TL; Ahern TP

**INSTITUCIÓN / INSTITUTION:** - Gitte Vrelits Sorensen, Lars Pedersen, Henrik Toft Sorensen, Deirdre Cronin-Fenton, Peer M. Christiansen, Timothy L. Lash, and Thomas P. Ahern, Aarhus University Hospital, Aarhus; Henrik Toft Sorensen

and Peer M. Christiansen, Danish Breast Cancer Cooperative Group, Copenhagen; Jens Peter Garne, Aalborg University Hospital, Aalborg, Denmark; Patricia A. Ganz and Steven W. Cole, University of California at Los Angeles, Los Angeles, CA; Timothy L. Lash, Rollins School of Public Health, Emory University, Atlanta, GA; and Thomas P. Ahern, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

**RESUMEN / SUMMARY:** - PURPOSE To estimate associations between use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) and breast cancer recurrence in a large Danish cohort. PATIENTS AND METHODS We enrolled 18,733 women diagnosed with nonmetastatic breast cancer between 1996 and 2003. Patient, treatment, and 10-year recurrence data were ascertained from the Danish Breast Cancer Cooperative Group registry. Prescription and medical histories were ascertained by linkage to the National Prescription Registry and Registry of Patients, respectively. beta-Blocker exposure was defined in aggregate and according to solubility, receptor selectivity, and individual drugs. ACE inhibitor and ARB exposures were defined in aggregate. Recurrence associations were estimated with multivariable Cox regression models in which time-varying drug exposures were lagged by 1 year. Results Compared with never users, users of any beta-blocker had a lower recurrence hazard in unadjusted models (unadjusted hazard ratio [HR] = 0.91; 95% CI, 0.81 to 1.0) and a slightly higher recurrence hazard in adjusted models (adjusted HR = 1.3; 95% CI, 1.1 to 1.5). Associations were similar for exposures defined by receptor selectivity and solubility. Although most individual beta-blockers showed no association with recurrence, metoprolol and sotalol were associated with increased recurrence rates (adjusted metoprolol HR = 1.5, 95% CI, 1.2 to 1.8; adjusted sotalol HR = 2.0, 95% CI, 0.99 to 4.0). ACE inhibitors were associated with a slightly increased recurrence hazard, whereas ARBs were not associated with recurrence (adjusted ACE inhibitor HR = 1.2, 95% CI, 0.97 to 1.4; adjusted ARBs HR = 1.1, 95% CI, 0.85 to 1.3). CONCLUSION Our data do not support the hypothesis that beta-blockers attenuate breast cancer recurrence risk.

[92]

**TÍTULO / TITLE:** - Molecular Mechanisms of the Cytotoxicity of Human alpha-Lactalbumin Made Lethal to Tumor Cells (HAMLET) and Other Protein-Oleic Acid Complexes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biol Chem. 2013 May 17;288(20):14408-16. doi: 10.1074/jbc.M112.437889. Epub 2013 Apr 11.

●● [Enlace al texto completo \(gratis o de pago\) 1074/jbc.M112.437889](#)

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**INSTITUCIÓN / INSTITUTION:** - From the Okazaki Institute for Integrative Bioscience and Institute for Molecular Science, National Institutes of Natural Sciences, 5-1 Higashiyama, Myodaiji, Okazaki 444-8787, Japan.

**RESUMEN / SUMMARY:** - Although HAMLET (human alpha-lactalbumin made lethal to tumor cells), a complex formed by human alpha-lactalbumin and oleic acid, has a unique apoptotic activity for the selective killing of tumor cells, the molecular mechanisms of expression of the HAMLET activity are not well understood. Therefore, we studied the molecular properties of HAMLET and its goat counterpart, GAMLET (goat alpha-lactalbumin made lethal to tumor cells), by pulse field gradient NMR and 920-MHz two-dimensional NMR techniques. We also examined the expression of HAMLET-like activities of complexes between oleic acid and other proteins that form a stable molten globule state. We observed that both HAMLET and GAMLET at pH 7.5 were heterogeneous, composed of the native protein, the monomeric molten globule-like state, and the oligomeric species. At pH 2.0 and 50 degrees C, HAMLET and GAMLET appeared in the monomeric state, and we identified the oleic acid-binding site in the complexes by two-dimensional NMR. Rather surprisingly, the binding site thus identified was markedly different between HAMLET and GAMLET. Furthermore, canine milk lysozyme, apo-myoglobin, and beta2-microglobulin all formed the HAMLET-like complex with the anti-tumor activity, when the protein was treated with oleic acid under conditions in which their molten globule states were stable. From these results, we conclude that the protein portion of HAMLET, GAMLET, and the other HAMLET-like protein-oleic acid complexes is not the origin of their cytotoxicity to tumor cells and that the protein portion of these complexes plays a role in the delivery of cytotoxic oleic acid molecules into tumor cells across the cell membrane.

[93]

**TÍTULO / TITLE:** - ERCC1 predicts outcome in patients with gastric cancer treated with adjuvant cisplatin-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 May 5.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2181-](#)

[2](#)

**AUTORES / AUTHORS:** - De Dosso S; Zanellato E; Nucifora M; Boldorini R; Sonzogni A; Biffi R; Fazio N; Bucci E; Beretta O; Crippa S; Saletti P; Frattini M

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**RESUMEN / SUMMARY:** - BACKGROUND: Adjuvant chemotherapy is gaining an increasing role in resectable gastric cancer. Customizing chemotherapy on the basis of chemosensitivity may improve outcome, and putative predictive molecular markers have been mostly evaluated in Asian patients. We profiled key DNA and damage signaling factors and correlated them with outcome, in a

European cohort. METHODS: Formalin-fixed tumor samples obtained from surgical specimens of patients treated with adjuvant cisplatin-based chemotherapy for gastric cancer were analyzed. Immunohistochemistry (IHC) was performed to analyze excision repair cross-complementing gene 1 (ERCC1) and thymidylate synthase (TS) expression, and p53 mutations were detected with direct sequencing. RESULTS: Among the 68 patient recruited, the median age was 69 (range 30-74), and UICC stage was III in 44 patients (65 %). With a median follow-up of 40.5 months, disease-free and overall survival were 18.0 (95 % CI 13.4-22.76) and 56 months (95 % CI 44.87-67.13), respectively. ERCC1 score was 0 in 14 out 67 (21 %) cases, 1 in 19 (28 %), 2 in 20 (30 %) and 3 in 14 cases (21 %). Longer overall survival ( $p = 0.04$ ) was found in patients categorized as ERCC1 negative by IHC according to median score. TS score was 0 in 16 out 67 (24 %) cases, 1 in 27 (40 %), 2 in 16 (24 %) and 3 in 8 cases (12 %). Mutations of p53 were found in 21 out 66 (32 %) cases. Neither TS nor p53 were found to correlate with outcome. CONCLUSION: Excision repair cross-complementing gene 1 by IHC might predict patients more likely to benefit from adjuvant cisplatin-based chemotherapy in curatively resected gastric cancer. In patients exhibiting ERCC1 positive tumors, alternative regimens should be evaluated.

[94]

**TÍTULO / TITLE:** - Time for a revision on the role of PSA response rate as a surrogate marker for median overall survival in docetaxel-based first-line treatment for patients with metastatic hormone-refractory prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biol Markers. 2013 Apr 15:0. doi: 10.5301/jbm.5000019.

●●Enlace al texto completo (gratis o de pago) [5301/jbm.5000019](#)

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**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Unit, University of Siena, Siena - Italy.

[95]

**TÍTULO / TITLE:** - Tau protein as a potential predictive marker in epithelial ovarian cancer patients treated with paclitaxel/platinum first-line chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Exp Clin Cancer Res. 2013 Apr 30;32:25. doi: 10.1186/1756-9966-32-25.

●●Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-25](#)

**AUTORES / AUTHORS:** - Smoter M; Bodnar L; Grala B; Stec R; Zieniuk K; Kozłowski W; Szczylik C

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**RESUMEN / SUMMARY:** - BACKGROUND: The aim of the study was to evaluate predictive and prognostic significance of microtubule-associated protein Tau in epithelial ovarian cancer (EOC) patients treated with paclitaxel and platinum-based chemotherapy. METHODS: 74 patients with EOC (stage I-IV) who underwent cytoreductive surgery followed by standard paclitaxel/platinum chemotherapy were included in the retrospective analysis. Their formalin-fixed, paraffin-embedded tissue specimens were immunohistochemically stained for Tau protein, using semi-quantitative DAKO test. Tau expression was acknowledged as negative (0 and 1+) or positive (2+ and 3+). The correlation between Tau expression, progression free survival (PFS) and overall survival (OS) was evaluated. Statistical analysis included Kaplan-Meier estimator, long rank test, Mann Whitney test and Cox proportional hazards model. RESULTS: 25.7% (19/74) and 74.3% (55/74) of the patients were classified as Tau-negative and Tau-positive, respectively. Median PFS was 28.7 months for Tau-negative group and 15.9 months for Tau-positive group ( $p = 0.0355$ ). In the univariate analysis 3-year OS in Tau-negative and Tau-positive groups was 80.2% and 52.4%, respectively ( $p = 0.0198$ ). Low expression of protein Tau was associated with better OS, whereas an advanced stage at diagnosis, suboptimal surgery, serous histological type and resistance to first line chemotherapy were each correlated with worse OS ( $p < 0,05$ ). In multivariate analysis only resistance to first line chemotherapy remained significant (HR 22.59; 95% CI, 8.71-58.55;  $p < 0.0001$ ). CONCLUSIONS: Negative tau protein seems to be both good prognostic factor and a predictor of response to paclitaxel/platinum-based chemotherapy in EOC patients.

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[96]

**TÍTULO / TITLE:** - Serum miR-21 as a Diagnostic and Prognostic Biomarker in Colorectal Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Natl Cancer Inst. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1093/jnci/djt101](#)

**AUTORES / AUTHORS:** - Toiyama Y; Takahashi M; Hur K; Nagasaka T; Tanaka K; Inoue Y; Kusunoki M; Boland CR; Goel A

**INSTITUCIÓN / INSTITUTION:** - Affiliations of authors: Gastrointestinal Cancer Research Laboratory, Division of Gastroenterology, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX (YT, MT, KH, CRB, AG); Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Graduate School of Medicine, Mie University, Mie, Japan (YT, KT, YI, MK); Department of Gastroenterological

Surgery and Surgical Oncology, Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan (TN).

**RESUMEN / SUMMARY:** - BACKGROUND: The oncogenic microRNAs (miRNAs) miR-21 and miR-31 negatively regulate tumor-suppressor genes. Their potential as serum biomarkers has not been determined in human colorectal cancer (CRC). METHODS: To determine whether miR-21 and miR-31 are secretory miRNAs, we screened expression in medium from 2 CRC cell lines, which was followed by serum analysis from 12 CRC patients and 12 control subjects. We validated expression of candidate miRNAs in serum samples from an independent cohort of 186 CRC patients, 60 postoperative patients, 43 advanced adenoma patients, and 53 control subjects. We analyzed miR-21 expression in 166 matched primary CRC tissues to determine whether serum miRNAs reflect expression in CRC. Patient survival analyses were performed by Kaplan-Meier analyses and Cox regression models. All statistical tests were two-sided. RESULTS: Although miR-21 was secreted from CRC cell lines and upregulated in serum of CRC patients, no statistically significant differences were observed in serum miR-31 expression between CRC patients and control subjects. In the validation cohort, miR-21 levels were statistically significantly elevated in preoperative serum from patients with adenomas ( $P < .001$ ) and CRCs ( $P < .001$ ). Importantly, miR-21 expression dropped in postoperative serum from patients who underwent curative surgery ( $P < .001$ ). Serum miR-21 levels robustly distinguished adenoma (area under the curve [AUC] = 0.813; 95% confidence interval [CI] = 0.691 to 0.910) and CRC (AUC = 0.919; 95% CI = 0.867 to 0.958) patients from control subjects. High miR-21 expression in serum and tissue was statistically significantly associated with tumor size, distant metastasis, and poor survival. Moreover, serum miR-21 was an independent prognostic marker for CRC (hazard ratio = 4.12; 95% CI = 1.10 to 15.4;  $P = .03$ ). CONCLUSIONS: Serum miR-21 is a promising biomarker for the early detection and prognosis of CRC.

[97]

**TÍTULO / TITLE:** - Anti-EGFR antibody cetuximab in refractory or relapsed multiple myeloma: A phase II prospective clinical trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 29.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.809074](#)

**AUTORES / AUTHORS:** - von Tresckow B; Boell B; Eichenauer DA; Beschorner D; Knop S; Goebeler ME; Marcus Chemnitz J; Hallek M; Engert A; Huebel K

[98]

**TÍTULO / TITLE:** - Influence of ABCB1 polymorphisms and docetaxel pharmacokinetics on pathological response to neoadjuvant chemotherapy in breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):421-8. doi: 10.1007/s10549-013-2545-7. Epub 2013 May 11.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2545-](#)

[7](#)

**AUTORES / AUTHORS:** - Levy P; Gligorov J; Antoine M; Rezai K; Levy E; Selle F; Saintigny P; Lokiec F; Avenin D; Beerblock K; Lotz JP; Bernaudin JF; Fajac A

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**RESUMEN / SUMMARY:** - We have previously reported an association between ABCB1 C3435T polymorphism and docetaxel pharmacokinetics in breast cancer patients. We therefore investigated whether these parameters could account for variations in pathological response. Five ABCB1 polymorphisms including C3435T polymorphism were analyzed in breast cancer patients receiving neoadjuvant chemotherapy with doxorubicin and docetaxel (n = 101). Pathological response was assessed using the Sataloff classification. Pharmacokinetic analysis was performed for the first course of docetaxel (n = 84). No significant association was found between ABCB1 polymorphisms or docetaxel pharmacokinetics and pathological complete response. C3435T genotype was an independent predictive factor of good response in breast (response >50 %, i.e., Sataloff T-A and T-B): OR: 4.6 (95 % CI: 1.3-16.1), p = 0.015, for TT patients versus CT and CC patients. Area under the plasma concentration-time curve (AUC) of docetaxel was the only independent predictive factor of the total absence of response in breast (Sataloff T-D): OR: 14.3, (95 % CI: 1.7-118), p = 0.015, for AUC of docetaxel <3,500 mug h/L versus >=3,500 mug h/L. These results suggest that C3435T polymorphism and docetaxel exposure are involved in the response to neoadjuvant chemotherapy in breast cancer patients and may be useful to optimize individualized therapy.

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[99]

**TÍTULO / TITLE:** - Circulating levels of transforming growth factor-betaeta (TGF-beta) and chemokine (C-X-C motif) ligand-1 (CXCL1) as predictors of distant seeding of circulating tumor cells in patients with metastatic breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1491-7.

**AUTORES / AUTHORS:** - Divella R; Daniele A; Savino E; Palma F; Bellizzi A; Giotta F; Simone G; Liocce M; Quaranta M; Paradiso A; Mazzocca A

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**RESUMEN / SUMMARY:** - BACKGROUND: The presence of circulating tumor cells (CTCs) in the peripheral blood is a prerequisite for the formation of distant metastases. Transforming growth factor-betaeta (TGF-beta) and Chemokine (C-X-C Motif) Ligand-1 (CXCL1) are cytokines involved in the colonization of distant sites by CTCs in several pre-clinical animal models. However, their role is poorly-investigated in patients with metastatic cancer. Here, we investigated whether circulating levels of TGF-beta and CXCL1 are predictors of CTC seeding in preferential distant sites in patients with metastatic breast cancer. MATERIALS AND METHODS: CTCs were isolated from the peripheral blood of 61 patients with metastatic breast cancer by immunomagnetic separation. Plasma samples were collected from the same patients and assayed for TGF-beta and CXCL1 by enzyme-linked immunoassay. RESULTS: Patients were grouped in CK1+/- (N<10), CK2+ (N >= 10<50) and CK3+ (N >= 50), according to the number (N) of cytokeratin 7/8-positive CTCs: the highest number of CK7/8-positive CTCs was detected in patients with negative Human epidermal growth factor receptor-2 (HER-2/NEU) status (p<0.0001) antigen, identified by the monoclonal antibody Ki-67 (Ki-67) >= 15% (p=0.003), Carcinoma antigen 15-3 (CA-15.3) >= 40 U/ml (p=0.004) and those with lung metastases (p=0.01). We found that elevated plasma concentrations of TGF-beta and CXCL1 are predictive for the detection of CTCs. In particular, patients with CK3+ CTCs and plasma concentrations of TGF-beta and CXCL1 higher than the median value had a poor prognosis in comparison to patients with CK1+/- CTCs and TGF-beta and CXCL1 concentrations below the median value. CONCLUSION: Our study shows that elevated circulating levels of TGF-beta and CXCL1 are associated with a poor prognosis, and higher detection of CTCs and propensity of these cells to seed lung metastases in patients with breast cancer.

[100]

**TÍTULO / TITLE:** - Toxicities Following Treatment with Bisphosphonates and Receptor Activator of Nuclear Factor-kappaB Ligand Inhibitors in Patients with Advanced Prostate Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur Urol. 2013 May 13. pii: S0302-2838(13)00481-8. doi: 10.1016/j.eururo.2013.05.015.

●●Enlace al texto completo (gratis o de pago)

[1016/j.eururo.2013.05.015](http://1016/j.eururo.2013.05.015)

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**RESUMEN / SUMMARY:** - **CONTEXT:** Advanced prostate cancer (PCa) is associated with skeletal complications, both as a result of bone metastases and because of fractures associated with fragility due to androgen-deprivation therapy (ADT). Osteoclast inhibitors are commonly used to reduce skeletal complications but are associated with a number of potential adverse events. **OBJECTIVE:** To review clinical trials of osteoclast inhibitors in advanced PCa, to discuss the adverse event profile of these agents, and to discuss strategies to address specific adverse events. **EVIDENCE ACQUISITION:** PubMed was searched for reports of clinical trials of osteoclast inhibitors in advanced PCa. As zoledronic acid and denosumab are used most commonly in this disease, these trials were the focus. The literature was reviewed to identify key publications addressing the prevention and management of adverse events associated with these drugs. **EVIDENCE SYNTHESIS:** The major findings of the trials and the adverse events are discussed. Prevention and management of common adverse events are addressed. **CONCLUSIONS:** Zoledronic acid prevents loss of bone mineral density associated with ADT and delays skeletal-related events in metastatic castration-resistant PCa (mCRPC). Denosumab reduces the incidence of fragility fractures associated with ADT, delays the onset of bone metastases in nonmetastatic castration-resistant disease, and is superior to zoledronic acid in the prevention of skeletal complications in mCRPC. Adverse events associated with both agents include osteonecrosis of the jaw and hypocalcemia. Hypocalcemia is more common with denosumab. Zoledronic acid requires dose modifications for renal insufficiency, is contraindicated in severe renal insufficiency, and has been associated with deterioration of renal function. Appropriate patient selection with close attention to dental health, supplementation with calcium and vitamin D, and monitoring of laboratory values are effective strategies to minimize the impact of adverse events associated with osteoclast inhibitors in advanced PCa.

[101]

**TÍTULO / TITLE:** - NUP98-NSD1 gene fusion and its related gene expression signature are strongly associated with a poor prognosis in pediatric acute myeloid leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genes Chromosomes Cancer. 2013 Jul;52(7):683-93. doi: 10.1002/gcc.22064. Epub 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1002/gcc.22064](http://1002/gcc.22064)

**AUTORES / AUTHORS:** - Shiba N; Ichikawa H; Taki T; Park MJ; Jo A; Mitani S; Kobayashi T; Shimada A; Sotomatsu M; Arakawa H; Adachi S; Tawa A; Horibe K; Tsuchida M; Hanada R; Tsukimoto I; Hayashi Y

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology/Oncology, Gunma Children's Medical Center, Shibukawa, Japan; Department of Pediatrics, Gunma University Graduate School of Medicine, Maebashi, Japan.

**RESUMEN / SUMMARY:** - The cryptic t(5;11)(q35;p15.5) creates a fusion gene between the NUP98 and NSD1 genes. To ascertain the significance of this gene fusion, we explored its frequency, clinical impact, and gene expression pattern using DNA microarray in pediatric acute myeloid leukemia (AML) patients. NUP98-NSD1 fusion transcripts were detected in 6 (4.8%) of 124 pediatric AML patients. Supervised hierarchical clustering analyses using probe sets that were differentially expressed in these patients detected a characteristic gene expression pattern, including 18 NUP98-NSD1-negative patients (NUP98-NSD1-like patients). In total, a NUP98-NSD1-related gene expression signature (NUP98-NSD1 signature) was found in 19% (24/124) and in 58% (15/26) of cytogenetically normal cases. Their 4-year overall survival (OS) and event-free survival (EFS) were poor (33.3% in NUP98-NSD1-positive and 38.9% in NUP98-NSD1-like patients) compared with 100 NUP98-NSD1 signature-negative patients (4-year OS: 86.0%, 4-year EFS: 72.0%). Interestingly, t(7;11)(p15;p15)/NUP98-HOXA13, t(6;11)(q27;q23)/MLL-MLLT4 and t(6;9)(p22;q34)/DEK-NUP214, which are known as poor prognostic markers, were found in NUP98-NSD1-like patients. Furthermore, another type of NUP98-NSD1 fusion transcript was identified by additional RT-PCR analyses using other primers in a NUP98-NSD1-like patient, revealing the significance of this signature to detect NUP98-NSD1 gene fusions and to identify a new poor prognostic subgroup in AML. © 2013 Wiley Periodicals, Inc.

[102]

**TÍTULO / TITLE:** - Prespecified Candidate Biomarkers Identify Follicular Lymphoma Patients Who Achieved Longer Progression-Free Survival with Bortezomib-Rituximab Versus Rituximab.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 1;19(9):2551-2561. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3069](#)

**AUTORES / AUTHORS:** - Coiffier B; Li W; Henitz ED; Karkera JD; Favis R; Gaffney D; Shapiro A; Theocharous P; Elsayed YA; van de Velde H; Schaffer ME; Osmanov EA; Hong X; Scheliga A; Mayer J; Offner F; Rule S; Teixeira A; Romejko-Jarosinska J; de Vos S; Crump M; Shpilberg O; Zinzani PL; Cakana A; Esseltine DL; Mulligan G; Ricci D

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Hematologie, Hospices Civils de Lyon and University Lyon 1, Lyon, France; Janssen Research and Development, Spring House, Pennsylvania; Janssen Research and Development, Raritan, New Jersey; David Geffen School of Medicine at the

University of California and Translational Oncology Research International, Los Angeles, California; Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts; Janssen Research and Development, High Wycombe; Department of Haematology, Derriford Hospital, Plymouth, United Kingdom; Dienst Hematologie, UZ Gent, Gent, Belgium; Janssen Research and Development, Beerse, Belgium; Cancer Research Center, Moscow, Russia; Cancer Hospital, FuDan University, Shanghai, China; Instituto Nacional de Cancer, Rio de Janeiro, Brazil; CEITEC Brno, and Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and School of Medicine, Masaryk University, Brno, Czech Republic; Hospitais da Universidade de Coimbra, Coimbra, Portugal; The Maria Sklodowska-Curie Memorial Institute and Cancer Centre, Warszawa, Poland; Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; Institute of Hematology, Rabin Medical Center, Petah Tikva, Israel; and Policlinico S. Orsola, Malpigli Istituto di Ematologia e Oncologia Medica, Bologna, Italy.

**RESUMEN / SUMMARY:** - PURPOSE: Identify subgroups of patients with relapsed/refractory follicular lymphoma deriving substantial progression-free survival (PFS) benefit with bortezomib-rituximab versus rituximab in the phase III LYM-3001 study. EXPERIMENTAL DESIGN: A total of 676 patients were randomized to five 5-week cycles of bortezomib-rituximab or rituximab. The primary end point was PFS; this prespecified analysis of candidate protein biomarkers and genes was an exploratory objective. Archived tumor tissue and whole blood samples were collected at baseline. Immunohistochemistry and genetic analyses were completed for 4 proteins and 8 genes. RESULTS: In initial pairwise analyses, using individual single-nucleotide polymorphism genotypes, one biomarker pair (PSMB1 P11A C/G heterozygote, low CD68 expression) was associated with a significant PFS benefit with bortezomib-rituximab versus rituximab, controlling for multiple comparison corrections. The pair was analyzed under dominant, recessive, and additive genetic models, with significant association with PFS seen under the dominant model (G/G+C/G). In patients carrying this biomarker pair [PSMB1 P11A G allele, low CD68 expression ( $\leq 50$  CD68-positive cells), population frequency: 43.6%], median PFS was 14.2 months with bortezomib-rituximab versus 9.1 months with rituximab (HR 0.47,  $P < 0.0001$ ), and there was a significant overall survival benefit (HR 0.49,  $P = 0.0461$ ). Response rates were higher and time to next antilymphoma therapy was longer in the bortezomib-rituximab group. In biomarker-negative patients, no significant efficacy differences were seen between treatment groups. Similar proportions of patients had high-risk features in the biomarker-positive and biomarker-negative subsets. CONCLUSIONS: Patients with PSMB1 P11A (G allele) and low CD68 expression seemed to have significantly longer PFS and greater clinical benefit with bortezomib-rituximab versus rituximab. Clin Cancer Res; 19(9); 2551-61. ©2013 AACR.

[103]

**TÍTULO / TITLE:** - Application of comorbidity indexes at baseline could be useful to predict rates of response in patients with chronic myeloid leukemia treated with imatinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 29.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.795650](#)

**AUTORES / AUTHORS:** - Breccia M; Salaroli A; Serrao A; Zacheo I; Saracino R; Alimena G

**INSTITUCIÓN / INSTITUTION:** - Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy.

[104]

**TÍTULO / TITLE:** - Quantified KLK15 Gene Expression Levels Discriminate Prostate Cancer From Benign Tumors and Constitute a Novel Independent Predictor of Disease Progression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Prostate. 2013 Apr 26. doi: 10.1002/pros.22667.

●●Enlace al texto completo (gratis o de pago) [1002/pros.22667](#)

**AUTORES / AUTHORS:** - Mavridis K; Stravodimos K; Scorilas A

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, University of Athens, Athens, Greece.

**RESUMEN / SUMMARY:** - BACKGROUND: Several transcript variants of the kallikrein-related peptidase 15 gene (KLK15) have been identified up to now. The classical KLK15 mRNA isoform encodes for a non-truncated, functional protein. Aberrant KLK15 expression is found in breast, ovarian, and prostate cancers. Our aim in this present study was the specific quantitative expression analysis of the classical KLK15 mRNA transcript in prostate tumors and the examination of its clinical significance in prostate cancer. METHODS: We isolated total RNA from 150 prostate tissue specimens and, following cDNA synthesis, the expression of KLK15 classical mRNA transcript was measured via quantitative Real-Time PCR using the TaqMan® chemistry. HPRT1 was used as a reference gene, and the absolute quantification approach, through the incorporation of standard curves, was applied for the calculation of normalized KLK15 expression. RESULTS: KLK15 expression levels were significantly upregulated in malignant compared to benign samples ( $P < 0.001$ ). The discriminatory value of KLK15 was confirmed by ROC curve and logistic regression analysis (both  $P < 0.001$ ). KLK15 was also associated with advanced pathological stage ( $P = 0.023$ ). KLK15-positive prostate cancer patients presented significantly shorter progression-free survival intervals, determined by biochemical relapse ( $P = 0.006$ ), compared to KLK15-negative ones. Multivariate Cox regression analysis revealed that KLK15 expression is

an independent predictor of biochemical recurrence (HR = 3.36, P = 0.038).  
CONCLUSIONS: The present study unravels the important role of quantified  
KLK15 classical mRNA expression levels as a novel biomarker helpful for the  
differential diagnosis and prognosis of prostate cancer patients. Prostate 9999:  
XX-XX, 2013. © 2013 Wiley Periodicals, Inc.

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[105]

**TÍTULO / TITLE:** - Catecholamine-Induced beta2-Adrenergic Receptor Activation  
Mediates Desensitization of Gastric Cancer Cells to Trastuzumab by  
Upregulating MUC4 Expression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Immunol. 2013 Jun 1;190(11):5600-8. doi:  
10.4049/jimmunol.1202364. Epub 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago) [4049/jimmunol.1202364](#)

**AUTORES / AUTHORS:** - Shi M; Yang Z; Hu M; Liu D; Hu Y; Qian L; Zhang W;  
Chen H; Guo L; Yu M; Song L; Ma Y; Guo N

**INSTITUCIÓN / INSTITUTION:** - Department of Pathophysiology, Institute of Basic  
Medical Sciences, Beijing 100850, People's Republic of China.

**RESUMEN / SUMMARY:** - Trastuzumab is currently used for patients with Her2(+)  
advanced gastric cancer. However, the response rate to trastuzumab among  
the patients is low. The molecular mechanisms underlying trastuzumab  
resistance in gastric cancer are unknown. Our in vitro data show that activation  
of beta2-adrenergic receptor (beta2-AR) triggered by catecholamine caused  
“targeting failure” of trastuzumab in gastric cancer cells. The antitumor activities  
of trastuzumab were significantly impeded by chronic catecholamine stimulation  
in gastric cancer cells and in the mice bearing human gastric cancer xenografts.  
Mechanistically, catecholamine induced upregulation of the MUC4 expression  
at both transcription and protein levels via activating STAT3 and ERK. The  
effects of catecholamine could be effectively blocked by beta2-AR antagonist  
ICI-118,551, indicating that beta2-AR-mediated signaling pathway plays a key  
role in upregulation of MUC4, which was previously demonstrated to interfere  
with the recognition and physical binding of trastuzumab to Her2 molecules.  
Moreover, a significant elevation of the MUC4 level was observed in the  
xenograft tissues in nude mice chronically treated with isoproterenol.  
Knockdown of MUC4 restored the binding activities of trastuzumab to Her2-  
overexpressing gastric cancer cells. In addition, coexpression of beta2-AR and  
MUC4 were observed in gastric cancer tissues. Our data indicated a novel  
trastuzumab resistance mechanism, by which catecholamine-induced beta2-AR  
activation mediates desensitization of gastric cancer cells to trastuzumab  
through upregulating the MUC4 expression.

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[106]

**TÍTULO / TITLE:** - A novel inhibitor of proteasome deubiquitinating activity renders tumor cells sensitive to TRAIL-mediated apoptosis by natural killer cells and T cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Immunol Immunother. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s00262-013-1439-](http://1007/s00262-013-1439-1)

[1](#)

**AUTORES / AUTHORS:** - Sarhan D; Wennerberg E; D'Arcy P; Gurajada D; Linder S; Lundqvist A

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology-Pathology, Cancer Center Karolinska, Karolinska Institutet, R8:01, 171 76, Stockholm, Sweden.

**RESUMEN / SUMMARY:** - The proteasome inhibitor bortezomib simultaneously renders tumor cells sensitive to killing by natural killer (NK) cells and resistant to killing by tumor-specific T cells. Here, we show that b-AP15, a novel inhibitor of proteasome deubiquitinating activity, sensitizes tumors to both NK and T cell-mediated killing. Exposure to b-AP15 significantly increased the susceptibility of tumor cell lines of various origins to NK ( $p < 0.0002$ ) and T cell ( $p = 0.02$ )-mediated cytotoxicity. Treatment with b-AP15 resulted in increased tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor-2 expression ( $p = 0.03$ ) and decreased cFLIP expression in tumor cells in vitro. In tumor-bearing SCID/Beige mice, treatment with b-AP15 followed by infusion of either human NK cells or tumor-specific T cells resulted in a significantly delayed tumor progression compared with mice treated with NK cells ( $p = 0.006$ ), T cells ( $p < 0.0001$ ) or b-AP15 alone ( $p = 0.003$ ). Combined infusion of NK and T cells in tumor-bearing BALB/c mice following treatment with b-AP15 resulted in a significantly prolonged long-term survival compared with mice treated with b-AP15 and NK or T cells ( $p \leq 0.01$ ). Our findings show that b-AP15-induced sensitization to TRAIL-mediated apoptosis could be used as a novel strategy to augment the anticancer effects of adoptively infused NK and T cells in patients with cancer.

[107]

**TÍTULO / TITLE:** - Urgent treatment of patients with metastatic melanoma using braf inhibitors in the absence of braf mutation status.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Jun;24(6):1712-3. doi: 10.1093/annonc/mdt167. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt167](http://1093/annonc/mdt167)

**AUTORES / AUTHORS:** - Nathan P; Sharma A; Lorigan P

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood.

[108]

**TÍTULO / TITLE:** - Small Molecule Inhibitors of ERCC1-XPF Protein-Protein Interaction Synergize Alkylating Agents in Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Pharmacol. 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1124/mol.112.082347](#)

**AUTORES / AUTHORS:** - Jordheim LP; Barakat KH; Heinrich-Balard L; Matera EL; Cros-Perrial E; Bouledrak K; El Sabeh R; Perez-Pineiro R; Wishart DS; Cohen R; Tuszynski J; Dumontet C

**INSTITUCIÓN / INSTITUTION:** - 1 CRCL;

**RESUMEN / SUMMARY:** - The benefit of cancer chemotherapy based on alkylating agents is limited due to the action of DNA repair enzymes which mitigate the damage induced by these agents. The interaction between the proteins ERCC1 and XPF, involves two major components of the nucleotide excision repair pathway. Here, novel inhibitors of this interaction were identified by virtual screening based on available structures using the National Cancer Institute (NCI) diversity set and a panel of DrugBank-small-molecules. Subsequently, experimental validation of the in silico screening was undertaken. Top hits were evaluated on A549 and HCT116 cancer cells. In particular, the compound labeled NSC130813 was shown to act synergistically with cisplatin and mitomycin C, to increase UVC mediated cytotoxicity, to modify DNA repair as indicated by the staining of phosphorylated H2AX and to disrupt interaction between ERCC1 and XPF in cells. In addition, using the Biacore technique, we showed that this compound interacts with the domain of XPF responsible for interaction with ERCC1. This study shows that small molecules targeting the protein-protein interaction of ERCC1 and XPF can be developed in order to enhance the effects of alkylating agents on cancer cells.

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[109]

**TÍTULO / TITLE:** - High-density Lipoprotein Profiling Changes in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Cohort Study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Rheumatol. 2013 Jun;40(6):825-30. doi: 10.3899/jrheum.121358. Epub 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [3899/jrheum.121358](#)

**AUTORES / AUTHORS:** - Jamnitski A; Levels JH; van den Oever IA; Nurmohamed MT

**INSTITUCIÓN / INSTITUTION:** - From the Jan van Breemen Research Institute; Academic Medical Centre Amsterdam; and VU University Medical Centre, Amsterdam, The Netherlands.

**RESUMEN / SUMMARY:** - OBJECTIVE: We investigated changes in high-density lipoprotein (HDL) profiling in patients with rheumatoid arthritis who started

treatment by taking tumor necrosis factor (TNF) inhibitors. The patients were stratified for European League Against Rheumatism (EULAR) response. METHODS: A group of 100 patients naive for TNF inhibitors at baseline were randomly selected from 204 adalimumab-treated and 203 etanercept-treated patients on the basis of their EULAR response. HDL profiling was measured using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry. RESULTS: In EULAR good responders, mass charged markers representing serum amyloid A (SAA-1 and -2) decreased significantly after 4 months' therapy. There were no significant differences in HDL profiling in EULAR nonresponders. CONCLUSION: Effective suppression of inflammation with TNF inhibitors results in favorable changes in HDL composition.

[110]

**TÍTULO / TITLE:** - Towards prediction of efficacy of chemotherapy: a proof of concept study in lung cancer patients using [11C]docetaxel and positron emission tomography.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3779](#)

**AUTORES / AUTHORS:** - van der Veldt AA; Lubberink M; Mathijssen RH; Loos W; Herder GJ; Greuter HN; Comans EF; Rutten H; Eriksson J; Windhorst AD; Hendrikse H; Postmus PE; Smit EF; Lammertsma AA

**INSTITUCIÓN / INSTITUTION:** - Nuclear Medicine & PET Research, VU University Medical Center.

**RESUMEN / SUMMARY:** - PURPOSE: Pharmacokinetics of docetaxel can be measured in vivo using positron emission tomography (PET) and a microdose of radiolabeled docetaxel ([11C]docetaxel). The objective of this study was to investigate whether a [11C]docetaxel PET microdosing study could predict tumor uptake of therapeutic doses of docetaxel. EXPERIMENTAL DESIGN: Docetaxel-naive lung cancer patients underwent two [11C]docetaxel PET scans; one after bolus injection of [11C]docetaxel and another during combined infusion of [11C]docetaxel and a therapeutic dose of docetaxel (75 mg\*m-2). Compartmental and spectral analyses were used to quantify [11C]docetaxel tumor kinetics. [11C]docetaxel PET measurements were used to estimate the area under the curve (AUC) of docetaxel in tumors. Tumor response was evaluated using computed tomography scans. RESULTS: Net rates of influx (Ki) of [11C]docetaxel in tumors were comparable during microdosing and therapeutic scans. [11C]docetaxel AUCTumor during the therapeutic scan could be predicted reliably using an impulse response function derived from the microdosing scan together with the plasma curve of [11C]docetaxel during the therapeutic scan. At 90 min, the accumulated amount of docetaxel in tumors was <1% of the total infused dose of docetaxel. [11C]docetaxel Ki derived from

the microdosing scan correlated with AUCTumor of docetaxel (Spearman's rho= 0.715; P= 0.004) during the therapeutic scan and with tumor response to docetaxel therapy (Spearman's rho= -0.800; P= 0.010). CONCLUSIONS: Microdosing data of [11C]docetaxel PET can be used to predict tumor uptake of docetaxel during chemotherapy. The present study provides a framework for investigating the PET microdosing concept for radiolabeled anticancer drugs in patients.

[111]

**TÍTULO / TITLE:** - The Prognostic Value of microRNAs Varies with Patient Race/Ethnicity and Stage of Colorectal Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3302](#)

**AUTORES / AUTHORS:** - Bovell LC; Shanmugam C; Putcha BD; Katkoori VR; Zhang B; Bae S; Singh KP; Grizzle WE; Manne U

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, University of Alabama at Birmingham.

**RESUMEN / SUMMARY:** - PURPOSE: MicroRNAs (miRNAs) have potential prognostic value for colorectal cancers (CRCs); however, their value based on patient race/ethnicity and pathologic stage has not been determined. The goal was to ascertain the prognostic value of 5 miRNAs with increased expression in CRCs of African American (Black) and non-Hispanic Caucasian (White) patients. EXPERIMENTAL DESIGN: TaqMan® qRT-PCR was used to quantify expression of miR-20a, miR-21, miR-106a, miR-181b, and miR-203 in paired normal and tumor CRC archival tissues collected from 106 Black and 239 White patients. The results were correlated with overall survival based on patient race/ethnicity and pathologic stage. Since decisions regarding adjuvant therapy are important for Stage III CRCs, and since miR-181b appeared to have prognostic value only for Stage III Black patients, we assessed its prognostic value in a separate cohort of Stage III CRCs of Blacks. RESULTS: All 5 miRNAs had higher expression in CRCs (>1.0-fold) than in corresponding normal tissues. High expression of miR-203 was associated with poor survival of Whites with Stage IV CRCs (HR=3.00, 95% CI=1.29-7.53), but in Blacks it was an indicator of poor survival of patients with Stage I and II CRCs (HR=5.63, 95% CI=1.03-30.64). Increased miR-21 expression correlated with poor prognosis for White Stage IV patients (HR=2.50, 95% CI=1.07-5.83). In both test and validation cohorts, high miR-181b expression correlated with poor survival of only Black patients with Stage III CRCs (HR=1.94, 95% CI=1.03-3.67). CONCLUSIONS: These preliminary findings suggest that the prognostic value of miRNAs in CRCs varies with patient race/ethnicity and stage of disease.

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[112]

**TÍTULO / TITLE:** - Epithelial Cell Adhesion Molecule-positive Circulating Tumor Cells as Predictive Biomarker in Patients With Prostate Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Urology. 2013 Jun;81(6):1303-7. doi: 10.1016/j.urology.2012.10.041. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago)

[1016/j.urology.2012.10.041](#)

**AUTORES / AUTHORS:** - Amato RJ; Melnikova V; Zhang Y; Liu W; Saxena S; Shah PK; Jensen BT; Torres KE; Davis DW

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology, Department of Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX. Electronic address: [robert.amato@uth.tmc.edu](mailto:robert.amato@uth.tmc.edu).

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To assess the use of circulating tumor cells (CTCs) as a longitudinal endpoint factor for clinical monitoring of patients with prostate cancer and to evaluate the association among the baseline CTC number, various clinical characteristics, and survival. **MATERIALS AND METHODS:** The CTCs were enumerated using the CellSearch Food and Drug Administration-cleared CTC kit in 202 patients with prostate cancer. Variables, including metastatic site, prostate-specific antigen level, Gleason score, testosterone level, and use of androgen treatment, were tested for association with the CTC number. The probability of patient survival over time was estimated using the Kaplan-Meier method. **RESULTS:** The baseline CTC numbers were strongly associated with survival ( $P < .0001$ ), with overall survival significantly poorer in patients with  $\geq 5$  CTCs. Significantly greater CTC numbers were observed in patients with bone metastasis (mean 41.12 CTCs) than in those with lymph node metastasis (mean 2.53 CTC,  $P = .026$ ). Analysis of the association between the CTC count and prostate-specific antigen level revealed a weak positive correlation (correlation coefficient  $r = 0.2695$ ,  $P = .0007$ ). The CTC number also correlated with the Gleason score ( $P = .0138$ ) and lower testosterone level ( $P < .0001$ ). Patients without androgen depletion had significantly lower CTC numbers (mean 2.70) than those with androgen depletion (mean 26.39,  $P < .0001$ ). **CONCLUSION:** The baseline CTC counts were predictive of patient survival and correlated significantly with the clinical characteristics of patients with prostate cancer. Our study results have confirmed previous findings that support the use of CTC enumeration as a prognostic biomarker for patients with prostate cancer.

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[113]

**TÍTULO / TITLE:** - Expression of cytoskeleton-associated protein 4 is related to lymphatic metastasis and indicates prognosis of intrahepatic cholangiocarcinoma patients after surgery resection.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 May 9. pii: S0304-3835(13)00371-6. doi: 10.1016/j.canlet.2013.05.003.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.05.003](#)

**AUTORES / AUTHORS:** - Li MH; Dong LW; Li SX; Tang GS; Pan YF; Zhang J; Wang H; Zhou HB; Tan YX; Hu HP; Wang HY

**INSTITUCIÓN / INSTITUTION:** - International Cooperation Laboratory on Signal Transduction, Eastern Hepatobiliary Surgery Institute, The Second Military Medical University, Shanghai, PR China; Department of Liver Medicine, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, PR China.

**RESUMEN / SUMMARY:** - The objective of the study was to investigate the clinical significance of CKAP4 in intrahepatic cholangiocellular carcinoma (ICC). CKAP4 expression was determined in a cohort containing 173 cases of ICC patients. We found that CKAP4 was overexpressed in the majority of ICC cases and was significantly associated with tumor size, distant metastasis, lymph node metastasis, UICC and TNM stage features. Kaplan-Meier and Cox regression data indicated that CKAP4 was correlated with favorable clinical outcome and was an independent predictor for overall survival (HR, 0.646; 95% CI, 0.463-0.900 [p=0.010]). Thus, CKAP4 may serve as a prognostic marker of ICC patients.

[114]

**TÍTULO / TITLE:** - Genome-wide association study of genetic predictors of overall survival for non-small cell lung cancer in never smokers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-4033](#)

**AUTORES / AUTHORS:** - Wu X; Wang L; Ye Y; Aakre JA; Pu X; Chang GC; Yang PC; Roth JA; Marks RS; Lippman SM; Chang JY; Lu C; Deschamps C; Su WC; Wang WC; Huang MS; Chang DW; Li Y; Pankratz VS; Minna JD; Hong WK; Hildebrandt MA; Hsiung CA; Yang P

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology, University of Texas MD Anderson Cancer Center.

**RESUMEN / SUMMARY:** - To identify the genetic factors that influence overall survival in never smokers who have non-small cell lung cancer (NSCLC), we performed a consistency meta-analysis study utilizing genome-wide association approaches for overall survival in 327 never smoker NSCLC patients from the

MD Anderson Cancer Center and 293 cases from the Mayo Clinic. We then performed a two-pronged validation of the top 25 variants that included additional validation in 1,256 NSCLC patients from Taiwan and assessment of expression quantitative trait loci (eQTL) and differential expression of genes surrounding the top loci in 70 tumors and matched normal tissues. A total of 94 loci were significant for overall survival in both MD Anderson and Mayo studies in the consistency meta-analysis phase, with the top 25 variants reaching a p-value of  $10^{-6}$ . Two variants of these 25 were also significant in the Taiwanese population: rs6901416 (HR:1.44, 95%CI:1.01-2.06) and rs10766739 (HR:1.23, 95%CI:1.00-1.51). These loci resulted in a reduction in median survival time of at least 8 and 5 months in three populations, respectively. An additional six variants (rs4237904, rs7976914, rs4970833, rs954785, rs485411, and rs10906104) were validated through eQTL analysis that identified significant correlations with expression levels of six genes (LEMD3, TMBIM, ATXN7L2, SHE, ITIH2, and NUDT5, respectively) in normal lung tissue. These genes were also significantly differentially expressed between the tumor and normal lung. These findings identify several novel, candidate prognostic markers for NSCLC in never smokers, with eQTL analysis suggesting a potential biological mechanism for a subset of these observed associations.

[115]

**TÍTULO / TITLE:** - Primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with non-small-cell lung cancer harboring TKI-sensitive EGFR mutations: an exploratory study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt127](#)

**AUTORES / AUTHORS:** - Lee JK; Shin JY; Kim S; Lee S; Park C; Kim JY; Koh Y; Keam B; Min HS; Kim TM; Jeon YK; Kim DW; Chung DH; Heo DS; Lee SH; Kim Ji

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Seoul National University Hospital, Seoul.

**RESUMEN / SUMMARY:** - BACKGROUND: The mechanism of primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR-mutant non-small-cell lung cancer (NSCLC) has not been clearly understood. PATIENTS AND METHODS: Eleven patients exhibiting primary resistance (disease progression <3 months) were identified among 197 consecutive NSCLC patients with TKI-sensitive EGFR mutations who received EGFR TKIs at Seoul National University Hospital. Treatment-naive tumors were examined for concurrent genetic alterations using fluorescence in situ hybridization and targeted deep sequencing of cancer-related genes. Deletion polymorphism of Bcl-2-interacting mediator of cell death (BIM) gene was examined to validate its predictive role for TKI outcome. RESULTS: The

median progression-free survival (PFS) for patients receiving EGFR TKIs was 11.9 months, and the response rate 78.8%. Among the 11 patients exhibiting primary resistance, a de novo T790M mutation was identified in one patient, and two exhibited mesenchymal-epithelial transition amplification and anaplastic lymphoma kinase fusion. Targeted deep sequencing identified no recurrent, coexistent drivers of NSCLC. Survival analysis revealed that patients with recurrent disease after surgery had a longer PFS than those with initial stage IV disease. However, BIM deletion polymorphism, line of treatment, EGFR genotype, and smoking were not predictive of PFS for EGFR TKIs. CONCLUSIONS: We identified coexistent genetic alterations of cancer-related genes that could explain primary resistance in a small proportion of patients. Our result suggests that the mechanism of primary resistance might be heterogeneous.

[116]

**TÍTULO / TITLE:** - Serum thymidine kinase 1 activity in solid tumor (breast and colorectal cancer) patients treated with adjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Lab Anal. 2013 May;27(3):220-6. doi: 10.1002/jcla.21587.

●●Enlace al texto completo (gratis o de pago) [1002/jcla.21587](#)

**AUTORES / AUTHORS:** - Bolayirli M; Papila C; Korkmaz GG; Papila B; Aydogan F; Karatas A; Uzun H

**INSTITUCIÓN / INSTITUTION:** - Central Biochemistry Laboratory, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey.

**RESUMEN / SUMMARY:** - BACKGROUND: The aim of this study was to evaluate the changing of TK1 (where TK is thymidine kinase) activity before and after adjuvant chemotherapy in patients with breast and colorectal cancer.

METHODS: The study included 16 breast cancer, 25 colorectal cancer, and 38 healthy volunteers as the control group. Blood samples were taken twice from each patient; first at the beginning of the chemotherapy and second after six cycles of chemotherapy. TK1 activity was measured enzyme immunoassay method. RESULTS: The mean TK1 activity in the breast and colorectal cancer was significantly higher than the controls. TK1 activity in the colorectal cancer was higher than the breast cancer but this difference was not significant. TK1 activity after six doses of chemotherapy was lower than baseline TK1 activity before the start of chemotherapy in breast and colorectal cancer. TK1 activity was positively correlated with CA15-3, before and after chemotherapy in patients with breast cancer. TK1 activity in the colorectal cancer was also positively correlated with CA19-9, before and after chemotherapy. The values for the cutoff point, sensitivity, specificity, and the area under curve were determined for TK1 as >44.36 Du/L, 68.29%, 100% and 0.819, respectively in all subjects. CONCLUSION: Our results showed that serum TK1 activity in

patients with breast and colorectal cancer was significantly higher than that of the healthy controls. Moreover, after the completion of chemotherapy the values were lower than baseline. Pretreatment TK1 activity should be considered as a useful marker for assessment tumor cell proliferation in breast and colorectal cancer. Further work is needed to understand TK1 activity better in large populations of patients with solid tumor.

[117]

**TÍTULO / TITLE:** - Antibiotic Therapy-Induced Remission of Bladder Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma Carrying t(11;18)(q21;q21) Apoptosis Inhibitor 2-MALT1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 20.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.46.4800](#)

**AUTORES / AUTHORS:** - Lucioni M; Nicola M; Riboni R; Croci GA; Rattotti S; Gotti M; Arcaini L; Paulli M; Cristina S; Valentini S; Martinengo C

**INSTITUCIÓN / INSTITUTION:** - University of Pavia and Istituto di Ricovero e Cure a Carattere Scientifico Fondazione Policlinico San Matteo, Pavia, Italy.

[118]

**TÍTULO / TITLE:** - Inhibition of Glycogen Synthase Kinase-3 Increases NKG2D Ligand MICA Expression and Sensitivity to NK Cell-Mediated Cytotoxicity in Multiple Myeloma Cells: Role of STAT3.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Immunol. 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [4049/jimmunol.1201426](#)

**AUTORES / AUTHORS:** - Fionda C; Malgarini G; Soriani A; Zingoni A; Cecere F; Iannitto ML; Ricciardi MR; Federico V; Petrucci MT; Santoni A; Cippitelli M

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Medicine, Cenci Bolognetti Foundation-Pasteur Institute, Sapienza University of Rome, 00161 Rome, Italy;

**RESUMEN / SUMMARY:** - Engagement of NKG2D and DNAM-1 accessory molecule-1 (DNAM-1) receptors on lymphocytes plays an important role for anticancer response and represents an interesting therapeutic target for pharmacological modulation. In this study, we investigated the effect of inhibitors targeting the glycogen synthase kinase-3 (GSK3) on the expression of NKG2D and DNAM-1 ligands in multiple myeloma (MM) cells. GSK3 is a pleiotropic serine-threonine kinase point of convergence of numerous cell-signaling pathways, able to regulate the proliferation and survival of cancer cells, including MM. We found that inhibition of GSK3 upregulates both MICA protein surface and mRNA expression in MM cells, with little or no effects on the basal expression of the MICB and DNAM-1 ligand poliovirus receptor/CD155.

Moreover, exposure to GSK3 inhibitors renders myeloma cells more efficient to activate NK cell degranulation and to enhance the ability of myeloma cells to trigger NK cell-mediated cytotoxicity. We could exclude that increased expression of beta-catenin or activation of the heat shock factor-1 (transcription factors inhibited by active GSK3) is involved in the upregulation of MICA expression, by using RNA interference or viral transduction of constitutive active forms. On the contrary, inhibition of GSK3 correlated with a downregulation of STAT3 activation, a negative regulator of MICA transcription. Both Tyr705 phosphorylation and binding of STAT3 on MICA promoter are reduced by GSK3 inhibitors; in addition, overexpression of a constitutively active form of STAT3 significantly inhibits MICA upregulation. Thus, we provide evidence that regulation of the NKG2D-ligand MICA expression may represent an additional immune-mediated mechanism supporting the antimyeloma activity of GSK3 inhibitors.

[119]

**TÍTULO / TITLE:** - Prognostic Role of p53 Messenger Ribonucleic Acid Expression in Patients after Curative Resection for Stage I to III Colorectal Cancer: Association with Colon Cancer Stem Cell Markers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Am Coll Surg. 2013 Jun;216(6):1063-9. doi: 10.1016/j.jamcollsurg.2013.01.058. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago)

[1016/j.jamcollsurg.2013.01.058](http://1016/j.jamcollsurg.2013.01.058)

**AUTORES / AUTHORS:** - Huh JW; Kim HR; Kim YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - **BACKGROUND:** The current study was performed to examine the prognostic role of p53 messenger ribonucleic acid (mRNA) expression in patients with colorectal cancer and analyze its relationship with the expression of CD44 and CD133 mRNA levels. **STUDY DESIGN:** We retrospectively reviewed 137 consecutive patients who underwent curative surgery for stage I to III colorectal cancer in 2006. Prognostic factors, including wild-type (wt) p53, cyclooxygenase-2, CD44, and CD133 mRNA levels, were determined using reverse transcriptase polymerase chain reaction and clinical outcomes were analyzed. **RESULTS:** Wild-type p53 mRNA expression was correlated with the expression of CD44 and CD133 mRNA ( $p = 0.005$  and  $p = 0.013$ , respectively). With a median follow-up period of 64 months, the 5-year disease-free survival rate of patients with elevated wt-p53 mRNA expression was significantly higher than that of those patients with low levels of wt-p53 mRNA expression (84.9% and 67.6%, respectively;  $p = 0.014$ ). A multivariate analysis identified 3 independent factors that substantially affected the disease-free survival: depth of tumor invasion, lymph node metastasis, and wt-p53

mRNA expression. The 5-year disease-free survival rate in patients with stage III or rectal tumors differed significantly between the low and high wt-p53 expression groups. In stage III cancers, high wt-p53 expression was associated with better survival than low wt-p53 expression in patients treated with adjuvant chemotherapy ( $p = 0.005$ ). A significant association between combined p53/CD44 expression and survival was evident ( $p = 0.006$ ). CONCLUSIONS: Expression of p53 mRNA is a useful predictor of survival in patients with stage III or rectal cancers, with a significant association with CD44 mRNA expression.

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[120]

**TÍTULO / TITLE:** - Protein-bound polysaccharide-K induces apoptosis via mitochondria and p38 mitogenactivated protein kinasedependent pathways in HL60 promyelomonocytic leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):99-104. doi: 10.3892/or.2013.2412. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2412](#)

**AUTORES / AUTHORS:** - Hirahara N; Edamatsu T; Fujieda A; Fujioka M; Wada T; Tajima Y

**INSTITUCIÓN / INSTITUTION:** - Department of Digestive and General Surgery, Shimane University Faculty of Medicine, Izumo, Shimane 6938501, Japan.

**RESUMEN / SUMMARY:** - Protein-bound polysaccharide-K (PSK) is extracted from *Coriolus versicolor* (CM101). PSK is a biological response modifier (BRM), and its mechanism of action is partly mediated by modulating host immune systems; however, recent studies showed antiproliferative activity of PSK. Therefore, we examined the mechanism underlying the antiproliferative activity of PSK using seven different human malignant cell lines (WiDr, HT29, SW480, KATO, AGS, HL-60 and U937), and PSK was found to inhibit the proliferation of HL-60 cells most profoundly. Therefore, HL-60 cells were used to elucidate the mechanism of the antiproliferative activity. Western blotting was performed to detect phosphorylated p38 mitogen-activated protein kinase (MAPK). A p38 MAPK inhibitor, SB203580, was used to examine the roles in PSK-induced apoptosis and growth inhibition. Flow cytometry was performed for mitochondrial membrane potential detection. PSK activated caspase-3 and induced p38 MAPK phosphorylation. Co-treatment with SB203580 blocked PSK-induced apoptosis, caspase-3 activation and growth inhibition. PSK induced apoptosis via the mitochondrial pathway. The depolarization of mitochondria induced by PSK was reversed by co-treatment with SB203580. The present study revealed that PSK induced apoptosis in HL-60 cells via a mitochondrial and p38 MAPK-dependent pathway.

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[121]

**TÍTULO / TITLE:** - Prognostic value of centromere protein-A expression in patients with epithelial ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0860-](http://1007/s13277-013-0860-6)

[6](#)

**AUTORES / AUTHORS:** - Qiu JJ; Guo JJ; Lv TJ; Jin HY; Ding JX; Feng WW; Zhang Y; Hua KQ

**INSTITUCIÓN / INSTITUTION:** - Department of Gynecology and Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Obstetrics and Gynecology Hospital of Fudan University, No. 419, Fangxie Rd, Shanghai, 200011, China.

**RESUMEN / SUMMARY:** - Altered expression of centromere protein-A (CENP-A) is observed in various types of human cancers. However, the clinical significance and pathological role of CENP-A in epithelial ovarian cancer (EOC) remains unclear. The main objective of this investigation was to clarify the relationships between CENP-A expression and the clinicopathological features of patients with EOC. Real-time quantitative PCR and Western blot were performed to examine CENP-A expression in 20 pairs of fresh-frozen EOC tissues and corresponding noncancerous tissues. Using immunohistochemistry, we performed a retrospective study of the CENP-A expression levels on 120 archival EOC paraffin-embedded samples. Prognostic outcomes correlated with CENP-A were examined using Kaplan-Meier analysis and Cox proportional hazards model. Our results showed that the expression levels of CENP-A mRNA and protein in EOC tissues were both significantly higher than those in noncancerous tissues. By immunohistochemistry, the data revealed that high CENP-A expression was significantly correlated with pathological grade ( $P = 0.02$ ) and International Federation of Gynecology and Obstetrics stage ( $P = 0.006$ ). Consistent with these results, we found that high expression of CENP-A was significantly correlated with poor survival in EOC patients ( $P < 0.001$ ). Furthermore, Cox regression analyses showed that CENP-A expression was an independent predictor of overall survival. Our data suggest that CENP-A could play an important role in EOC and might serve as a valuable prognostic marker and potential target for gene therapy in the treatment of EOC.

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[122]

**TÍTULO / TITLE:** - A patient-derived somatic mutation in the epidermal growth factor receptor ligand-binding domain confers increased sensitivity to cetuximab in head and neck cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Jul;49(10):2345-55. doi: 10.1016/j.ejca.2013.03.005. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.03.005](http://1016/j.ejca.2013.03.005)

**AUTORES / AUTHORS:** - Bahassi el M; Li YQ; Wise-Draper TM; Deng L; Wang J; Darnell CN; Wilson KM; Wells SI; Stambrook PJ; Rixe O

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Division of Hematology/Oncology, UC Cancer Institute, University of Cincinnati, Cincinnati, OH, USA. Electronic address: [bhassiem@uc.edu](mailto:bhassiem@uc.edu).

**RESUMEN / SUMMARY:** - **BACKGROUND:** Cetuximab is an epidermal growth factor receptor (EGFR)-blocking antibody that has been approved for the treatment of patients with head and neck squamous cell carcinoma (HNSCC) and metastatic colorectal cancer, but no predictive biomarkers of activity have been yet identified. Establishment of such biomarkers will help identify a subset of patients that will benefit from cetuximab therapy. **METHODS:** In this paper, we report on a patient with HNSCC who had a complete tumour regression following treatment with cetuximab given as a single agent after initial surgery and radiation therapy. The EGFR protein expression level, the EGFR gene copy number and the EGFR gene sequence were assessed from both normal and tumour tissues. **RESULTS:** Besides protein overexpression and gene amplification in the tumour tissue, sequencing of the EGFR gene from the patient revealed the presence of two somatic mutations, one in the kinase domain (R705G) and the other in the ligand binding domain (P546S). Cells that stably express these EGFR mutants were treated with cetuximab and their sensitivity to the drug was compared to cells expressing the wildtype gene. While P546S mutation sensitised NIH-3T3 cells to cetuximab, R705G had a marginal effect. The double mutant (P546S/R705G) behaved like the P546S mutant, indicating that the mutation in the kinase domain does not contribute to the increased sensitivity to cetuximab. No mutations were found in K-RAS or B-RAF genes and no HPV protein or DNA was detected in the tumour. This is the first report of a somatic mutation in the EGFR ligand binding domain that may contribute to increased sensitivity to cetuximab. **CONCLUSIONS:** Our results support a role for the P546S mutation in cetuximab sensitivity. Other factors including EGFR protein high copy number and protein overexpression may have also contributed to the observed response. The severity of a skin rash developed by this patient and its correlation with the antitumour activity does not exclude the involvement of the immune system (i.e. complement-mediated immune response) as well. The occurrence of the P546S mutation needs to be evaluated in HNSCC, as a well as a prospective evaluation of cetuximab anti-tumour activity in patients with tumours harbouring the mutation.

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[123]

**TÍTULO / TITLE:** - Magnetic resonance imaging enhancement features before and after neoadjuvant chemotherapy in patients with breast cancer: a predictive value for responders.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Comput Assist Tomogr. 2013 May-Jun;37(3):432-9. doi: 10.1097/RCT.0b013e31828386ae.

●●Enlace al texto completo (gratis o de pago)

[1097/RCT.0b013e31828386ae](https://doi.org/10.1097/RCT.0b013e31828386ae)

**AUTORES / AUTHORS:** - Kang DK; Kim TH; Han TS; Kim KS; Yim H

**INSTITUCIÓN / INSTITUTION:** - From the Departments of \*Radiology, daggerSurgery, and double daggerPathology, Ajou University School of Medicine, Suwon, Gyeonggi, South Korea.

**RESUMEN / SUMMARY:** - **PURPOSE:** This study examined the ability of magnetic resonance imaging (MRI) enhancement features to predict the response to neoadjuvant chemotherapy (NAC) in patients with breast cancer. **METHODS:** This retrospective study included 107 patients with breast cancer. All patients underwent a baseline breast MRI before NAC and follow-up MRI a mean of 3.7 months later. Breast MRI scans were evaluated using the Breast Imaging Reporting and Data System MRI lexicon. In addition, whole-breast vascularity (WBV) in the cancer-bearing breast was graded according to increased vessel number in comparison with the contralateral breast. Histopathologic tumor regression was graded semiquantitatively based on the Miller-Payne grading system. The ability of each MRI feature to predict the response was evaluated using a logistic regression analysis. Correlations between changes in MRI features and response were also evaluated using the Spearman rank correlation test. **RESULTS:** There were 73 responders (68%), including 59 partial and 14 complete responders. No significant difference in baseline MRI features was found between the responders and nonresponders, except for tumor size ( $P = 0.044$ ). No dynamic enhancement feature on baseline MRI was useful for the early prediction of a response. In addition, an increased WBV did not predict a response, and the WBV change on the follow-up MRI was not correlated with the response. However, the change in the initial enhancement pattern ( $P = 0.007$ ) and kinetic curve type ( $P = 0.003$ ) were significantly correlated with response. **CONCLUSIONS:** No baseline MRI feature described using the Breast Imaging Reporting and Data System MRI lexicon was useful for early prediction of the response to NAC.

[124]

**TÍTULO / TITLE:** - Diffusion-weighted MRI in pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur Radiol. 2013 May 8.

●●Enlace al texto completo (gratis o de pago) [1007/s00330-013-2850-](https://doi.org/10.1007/s00330-013-2850-x)

[X](#)

**AUTORES / AUTHORS:** - Richard R; Thomassin I; Chapellier M; Scemama A; de Cremoux P; Varna M; Giacchetti S; Espie M; de Kerviler E; de Bazelaire C

**INSTITUCIÓN / INSTITUTION:** - Radiology Department, Saint-Louis Hospital, 1 avenue Claude Vellefaux, 75010, Paris, France, [raphmed@hotmail.com](mailto:raphmed@hotmail.com).

**RESUMEN / SUMMARY:** - PURPOSE: To evaluate the accuracy of the apparent diffusion coefficient (ADC) provided by diffusion-weighted imaging (DWI) in predicting the response to neoadjuvant chemotherapy (NACT) at baseline in patients according to their breast tumour phenotypes. MATERIALS & METHODS: This retrospective study was approved by our institutional review board. One hundred eighteen consecutive women with locally advanced breast cancer who had undergone NACT followed by breast surgery were included. DWI was performed at 1.5 T less than 2 weeks before NACT. We studied the correlation between pretreatment ADC and response in pathology after surgery according to immunohistochemical features and intrinsic subtypes (luminal A, luminal B, HER2-enriched, and triple-negative tumours). RESULTS: After surgery, the pathologist recognized 24 complete responders (CRps) and 94 non-complete responders (NCRps). No difference was identified between the pretreatment ADCs of the CRp and NCRp patients. There were differences in pretreatment ADCs among the luminal A ( $1.001 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{s}$ ), luminal B ( $0.983 \pm 0.150 \times 10^{-3} \text{ mm}^2/\text{s}$ ), HER2-enriched ( $1.132 \pm 0.216 \times 10^{-3} \text{ mm}^2/\text{s}$ ), and triple-negative ( $1.168 \pm 0.245 \times 10^{-3} \text{ mm}^2/\text{s}$ ;  $P = 0.0003$ ) tumour subtypes. In triple-negative tumours, the pretreatment ADC was higher in NCRp ( $1.060 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{s}$ ) than in CRp patients ( $1.227 \pm 0.271 \times 10^{-3} \text{ mm}^2/\text{s}$ ;  $P = 0.047$ ). CONCLUSION: Pretreatment ADC can predict the response of breast cancer to NACT if tumour subtypes are considered. Key Points \* Apparent diffusion coefficient helps clinicians to assess patients with breast cancer. \* Pretreatment ADC is related to tumour grade and hormone receptor status. \* Pretreatment ADC is lower in luminal A and B than in triple-negative tumours. \* Pretreatment ADC is higher in complete than in non-complete responders to neoadjuvant chemotherapy.

[125]

**TÍTULO / TITLE:** - Pre-existing IgG antibodies cross-reacting with the Fab region of infliximab predict efficacy and safety of infliximab therapy in inflammatory bowel disease.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Aliment Pharmacol Ther. 2013 Jun;37(12):1172-83. doi: 10.1111/apt.12330. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1111/apt.12330](http://1111/apt.12330)

**AUTORES / AUTHORS:** - Steenholdt C; Palarasah Y; Bendtzen K; Teisner A; Brynskov J; Teisner B; Nielsen CH

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Herlev Hospital, Herlev, Denmark.

**RESUMEN / SUMMARY:** - BACKGROUND: Infliximab (IFX) is a chimeric murine/human anti-TNF antibody (Ab) used for the treatment of Crohn's disease

(CD) and ulcerative colitis (UC). Loss of response is common and associated with development of anti-IFX Abs during ongoing therapy. However, human anti-murine immunoglobulin Abs are common and may cross-react with the murine part of IFX. AIM: To investigate if Abs binding to IFX's Fab region (IFX-Fab) are present in IBD patients before exposure to IFX, and whether they predict efficacy and safety of IFX therapy. METHODS: Observational, retrospective cohort study of patients with CD (n = 29) and UC (n = 22). RESULTS: Pre-treatment levels of IFX-Fab reactive IgG Abs were significantly lower in CD patients in remission after 1 year of maintenance IFX (median 91 mU/L, n = 8) than in the rest of the patients (639 mU/L, n = 21; P < 0.01), and lower than in patients with secondary loss of response in particular (692 mU/L, n = 7; P < 0.01). A cut-off concentration of <439 mU IFX-Fab reactive IgG Ab per litre comprised all patients who later obtained long-term sustained remission on IFX (sensitivity 100%, specificity 67%). Similar trends were observed in UC. The pre-treatment levels of IFX-Fab reactive IgG Abs were markedly higher in patients developing infusion reactions to IFX (1037 mU/L, n = 7) than in the remaining patients (349 mU/L, n = 44; P = 0.036). CONCLUSIONS: IFX-Fab reactive IgG antibodies present in serum from IBD patients before infliximab therapy associate with lack of long-term efficacy and safety. Assessments of such antibodies may help clinicians to choose between treatment with infliximab and more humanised agents.

[126]

**TÍTULO / TITLE:** - Increased pathological complete response rate after a long-term neoadjuvant letrozole treatment in postmenopausal oestrogen and/or progesterone receptor-positive breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Apr 30;108(8):1587-92. doi: 10.1038/bjc.2013.151. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.151](#)

**AUTORES / AUTHORS:** - Allevi G; Strina C; Andreis D; Zanoni V; Bazzola L; Bonardi S; Foroni C; Milani M; Cappelletti MR; Gussago F; Aguggini S; Giardini R; Martinotti M; Fox SB; Harris AL; Bottini A; Berruti A; Generali D

**INSTITUCIÓN / INSTITUTION:** - U.O. Multidisciplinare di Patologia Mammaria, Laboratorio di Oncologia Molecolare Senologica, A.O. Istituti Ospitalieri di Cremona, Viale Concordia 1, Cremona 26100, Italy.

**RESUMEN / SUMMARY:** - Background:The objective of this study was to determine the optimal scheduling of 2.5 mg daily letrozole in neoadjuvant breast cancer patients to obtain pathological complete response (pathCR) and assess Ki-67 expression as an early predictor of response.Patients and methods:This single institution study comprised 120 oestrogen receptor (ER)-positive postmenopausal women with primary breast cancer (clinical stage  $\geq$ T2, N0-1), from three sequential cohorts (cohort A of 40, cohort B of 40 and cohort C of

40 patients, respectively) based on different duration of the neoadjuvant letrozole. Biological markers such as ER, progesterone receptor, HER2 and Ki-67 expression were tested at diagnosis and at definitive surgery. Results: A total of 89 patients (75.4%) achieved an objective response with 44 (37.3%) clinical CRs and 45 (38.1%) partial responses. The clinical CRs were significantly observed in cohort C (23 out of 40 patients, 57.5%) and B (16 out of 38 patients, 42.1%) compared with cohort A (5 out of 40 patients, 12.5%) (P-value for trend <0.001). Letrozole induced a similar significant reduction in Ki-67 index after treatment in all cohorts. The pathCR rate was significantly more frequent in cohort C (7 out of 40 patients, 17.5%) than in cohort A (1 out of 40 patients, 2.5%) and B (2 out of 40 patients, 5.0%) (P-value for trend <0.04). Conclusion: One-year neoadjuvant letrozole therapy leads to a higher pathCR rate and may be the optimal length of drug exposure.

[127]

**TÍTULO / TITLE:** - Metronomic chemotherapy following the maximum tolerated dose is an effective anti-tumour therapy affecting angiogenesis, tumour dissemination and cancer stem cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 May 7. doi: 10.1002/ijc.28259.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ijc.28259](#)

**AUTORES / AUTHORS:** - Vives M; Ginesta MM; Gracova K; Graupera M; Casanovas O; Capella G; Serrano T; Laquente B; Vinals F

**INSTITUCIÓN / INSTITUTION:** - Translational Research Laboratory, Catalan Institute of Oncology, IDIBELL, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Barcelona, España.

**RESUMEN / SUMMARY:** - In this article, the effectiveness of a multi-targeted chemo-switch (C-S) schedule that combines metronomic chemotherapy (MET) after treatment with the maximum tolerated dose (MTD) is reported. This schedule was tested with gemcitabine in two distinct human pancreatic adenocarcinoma orthotopic models and with cyclophosphamide in an orthotopic ovarian cancer model. In both models, the C-S schedule had the most favourable effect, achieving at least 80% tumour growth inhibition without increased toxicity. Moreover, in the pancreatic cancer model, although peritoneal metastases were observed in control and MTD groups, no dissemination was observed in the MET and C-S groups. C-S treatment caused a decrease in angiogenesis, and its effect on tumour growth was similar to that produced by the MTD followed by anti-angiogenic DC101 treatment. C-S treatment combined an increase in thrombospondin-1 expression with a decrease in the number of CD133+ cancer cells and triple-positive CD133+/CD44+/CD24+ cancer stem cells (CSCs). These findings confirm that the C-S schedule is a challenging clinical strategy with demonstrable inhibitory effects on tumour dissemination, angiogenesis and CSCs.

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[128]

**TÍTULO / TITLE:** - Anticancer activities of anti-membrane antibodies against colon carcinoma cells undergoing chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumori. 2013 Jan-Feb;99(1):113-20. doi: 10.1700/1248.13798.

●●Enlace al texto completo (gratis o de pago) [1700/1248.13798](#)

**AUTORES / AUTHORS:** - Huang C; Zhu Y; Jiang Y; Li Z; Yao J; Duan G; Li D; Wang Q

**INSTITUCIÓN / INSTITUTION:** - Affiliated Hospital with Hangzhou Normal University School of Medicine, Hangzhou, China. [hcx588@hotmail.com](mailto:hcx588@hotmail.com)

**RESUMEN / SUMMARY:** - AIMS AND BACKGROUND: Chemotherapy combined with target therapy using antibodies against tumor cell membrane antigens may greatly increase the survival of cancer patients. Similar to autoantigens in autoimmunity diseases, certain membrane components may be more heterogeneous and create new determinants of antigens or haptens after chemotherapy. The aim of the current study was to prepare anti-membrane antibodies against colon carcinoma cells undergoing chemotherapy and examine their anticancer activities in vitro. METHODS: After the colon carcinoma cells were treated by mimic chemotherapy, the synthesized poly-lysine was used as a carrier to link the membrane antigen or hapten with the covalent bond of carbodiimide bridging. It was affirmed by fluorescence-activated cell sorting under laser confocal microscopy that the vaccine with poly-lysine membrane-linked cells with a covalent bond was successfully engineered. Then, the cognate mice were vaccinated, and the anti-membrane polyclonal antibodies were prepared and validated for their activities. RESULTS: The anti-membrane polyclonal antibodies were effectively induced and prepared. Folliculus lymphaticus were found significantly increased in vaccinated mice, and B lymphocyte proliferation was also intensively stimulated by vaccine and generating antibodies. The polyclonal antibodies, exhibiting minimal endotoxicity, displayed intensive sensitivity, high affinity and strong specificity. They also elicited apoptosis and necrosis for wild type colon carcinoma cells and offered synergistic effect to repress the chemotherapy-resistant tumor cells. CONCLUSIONS: The poly-lysine-linked membrane for colon carcinoma cells undergoing chemotherapy could produce the anti-membrane polyclonal antibodies (promising as novel antibody molecules for target therapy) and generate an effective immune attack on the surviving cancer cells.

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[129]

**TÍTULO / TITLE:** - Deregulation of Apoptotic Factors Bcl-xL and Bax Confers Apoptotic Resistance to Myeloid-Derived Suppressive Cells and Contributes to their Persistence in Tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biol Chem. 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [1074/jbc.M112.434530](http://1074/jbc.M112.434530)

**AUTORES / AUTHORS:** - Hu X; Bardhan K; Paschall AV; Yang D; Waller JL; Park MA; Nayak-Kapoor A; Samuel TA; Abrams SI; Liu K

**INSTITUCIÓN / INSTITUTION:** - Georgia Health Sciences University, United States;

**RESUMEN / SUMMARY:** - Myeloid-derived suppressive cells (MDSCs) are heterogeneous immature myeloid cells that accumulate in response to tumor progression. Compelling data from mouse models and human cancer patients showed that tumor-induced inflammatory mediators induce MDSC differentiation. However, the mechanisms underlying MDSC persistence is largely unknown. Here, we demonstrated that tumor-induced MDSCs exhibit significantly decreased spontaneous apoptosis as compared to myeloid cells with the same phenotype from tumor-free mice. Consistent with the decreased apoptosis, cell surface Fas receptor decreased significantly in tumor-induced MDSCs. Screening for changes of key apoptosis mediators downstream the Fas receptor revealed that expression levels of IRF8 and Bax are diminished, whereas expression of Bcl-xL is increased in tumor-induced MDSCs. We further determined that IRF8 binds directly to Bax and Bcl-x promoter in primary myeloid cells in vivo, and IRF8-deficient MDSCs-like cells also exhibit increased Bcl-xL and decreased Bax expression. Analysis of CD69 and CD25 levels revealed that cytotoxic T lymphocytes (CTLs) are partially activated in tumor-bearing host. Strikingly, FasL but not perforin and granzymes were selectively activated in CTLs in the tumor-bearing host. ABT-737 significantly increased the sensitivity of MDSCs to Fas-mediated apoptosis in vitro. More importantly, ABT-737 therapy increased MDSCs spontaneous apoptosis and decreased MDSC accumulation in tumor-bearing mice. Our data thus determined that MDSCs use down-regulation of IRF8 to alter Bax and Bcl-xL expression to deregulate the Fas-mediated apoptosis pathway to evade elimination by host CTLs. Therefore, targeting Bcl-xL is potentially effective in suppression of MDSC persistence in cancer therapy.

[130]

**TÍTULO / TITLE:** - Global methylation analysis identifies prognostically important epigenetically inactivated tumour suppressor genes in multiple myeloma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-03-487884](http://1182/blood-2013-03-487884)

**AUTORES / AUTHORS:** - Kaiser MF; Johnson DC; Wu P; Walker BA; Brioli A; Mirabella F; Wardell CP; Melchor L; Davies FE; Morgan GJ

**INSTITUCIÓN / INSTITUTION:** - Haemato-Oncology Research Unit, Division of Molecular Pathology, The Institute of Cancer Research, London, United Kingdom.

**RESUMEN / SUMMARY:** - Outcome in multiple myeloma is highly variable and a better understanding of the factors that influence disease biology is essential to understand and predict behaviour in individual patients. In the present study we analysed combined genome wide DNA methylation and gene expression data of patients treated in the MRC Myeloma IX trial. We used this data to identify epigenetically repressed tumour suppressor genes with prognostic relevance in myeloma. We identified 195 genes with changes in methylation status that were significantly associated with prognosis. Combining DNA methylation and gene expression data led to the identification of the epigenetically regulated tumour modulating genes GPX3, RBP1, SPARC and TGFBI. Hypermethylation of these genes was associated with significantly shorter overall survival, independent of age, ISS score and adverse cytogenetics. The four differentially methylated and expressed genes are known to mediate important tumour suppressive functions including response to chemotherapy (TGFBI), interaction with the microenvironment (SPARC), retinoic acid signalling (RBP1) and the response to oxidative stress (GPX3), which could explain the prognostic impact of their differential methylation. Assessment of the DNA methylation status of the identified genes could contribute to the molecular characterisation of myeloma, which is prerequisite for an individualised treatment approach.

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[131]

**TÍTULO / TITLE:** - Prognostic value of tissue protein expression levels of MIB-1 (Ki-67) in Danish ovarian cancer patients. From the 'MALOVA' ovarian cancer study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - APMIS. 2013 Apr 18. doi: 10.1111/apm.12071.

●●Enlace al texto completo (gratis o de pago) [1111/apm.12071](http://1111/apm.12071)

**AUTORES / AUTHORS:** - Heeran MC; Hogdall CK; Kjaer SK; Christensen L; Jensen A; Blaakaer J; Christensen IJ; Hogdall EV

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Herlev Hospital, Aarhus, Denmark.

**RESUMEN / SUMMARY:** - The primary objective of this study was to assess the expression of MIB-1 (Ki-67) in tumour tissues from 808 patients with epithelial ovarian tumours. The second was to evaluate, whether MIB-1 (Ki-67) tissue expression levels correlate with clinicopathological parameters and prognosis of the disease. Using tissue arrays (TA), we analysed the MIB-1 (Ki-67) expression levels in tissues from 202 women with borderline ovarian tumours (BOT) (177 stage I, 5 stage II, 19 stage III, 1 stage IV) and 606 ovarian cancer

(OC) patients (177 stage I, 64 stage II, 311 stage III, 54 stage IV). Using a 10% cut-off level for MIB-1 (Ki-67) overexpression, 12% of the BOTs and 51% of the OCs were positive for MIB-1 (Ki-67) expression. The frequency of MIB-1 (Ki-67) expression-positive OC increased with increasing FIGO stage ( $p = 0.003$ ), increasing histological grade ( $p \leq 0.0001$ ), and a significantly different distribution of MIB-1 (Ki-67) positive and negative tumours were found in adenocarcinoma NOS, serous adenocarcinomas, mucinous adenocarcinomas, endometrioid adenocarcinomas, non-epithelial and clear-cell carcinomas ( $p = 0.016$ ). Univariate Kaplan-Meier survival analysis performed on all OC cases showed a significant shorter disease specific survival in patients with positive MIB-1 (Ki-67) expression in the tumour tissue ( $p \leq 0.0001$ ). In a Cox survival analysis including 606 FIGO stages I to IV OC cases, FIGO stage (II vs I: HR = 3.00, 95% CI: 1.81-4.99, III-I: HR = 6.41, 95% CI: 3.90-10.50, IV vs I: HR = 12.69, 95% CI: 7.21-22); age at diagnosis  $\geq 10$  years (HR = 1.27, 95% CI: 1.15-1.40), residual tumour after surgery (HR = 1.95, 95% CI: 1.40-2.73) and MIB-1 (Ki-67) expression (HR = 1.31, 95% CI: 1.08-1.60) had a significant independent impact on survival. Histological grade ( $p = 0.14$ ) and histological tumour type ( $p = 0.35$ ) had no significant independent impact on survival. In conclusion, our results predict that an increased level of MIB-1 (Ki-67) expression in tumour tissue, points to a less favourable outcome for OC patients.

[132]

**TÍTULO / TITLE:** - Transcriptional repression of AIB1 by FoxG1 leads to apoptosis in breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Endocrinol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1210/me.2012-1353](#)

**AUTORES / AUTHORS:** - Li JV; Chien CD; Garee JP; Xu J; Wellstein A; Riegel AT

**INSTITUCIÓN / INSTITUTION:** - 1Departments of Pharmacology and Oncology, Lombardi Cancer Center, Georgetown University Medical Center, WA, DC 20007;

**RESUMEN / SUMMARY:** - The oncogene nuclear receptor coactivator amplified in breast cancer 1 (AIB1) is a transcriptional coactivator that is overexpressed in various types of human cancers. However, the molecular mechanisms controlling AIB1 expression in the majority of cancers remain unclear. In this study, we identified a novel interacting protein of AIB1, forkhead-box protein G1 (FoxG1), which is an evolutionarily conserved forkhead-box transcriptional corepressor. We show that FoxG1 expression is low in breast cancer cell lines, and that low levels of FoxG1 are correlated with a worse prognosis in breast cancer. We also demonstrate that transient overexpression of FoxG1 can suppress endogenous levels of AIB1 mRNA and protein in MCF-7 breast cancer cells. Exogenously expressed FoxG1 in MCF-7 cells also leads to

apoptosis that can be rescued in part by AIB1 overexpression. Using chromatin immunoprecipitation (ChIP), we determined that FoxG1 is recruited to a region of the AIB1 gene promoter previously characterized to be responsible for AIB1-induced, positive auto-regulation of transcription through the recruitment of an activating, multiprotein complex, involving AIB1, E2F1 and Sp1. Increased FoxG1 expression significantly reduces the recruitment of AIB1, E2F1 and p300 to this region of the endogenous AIB1 gene promoter. Our data imply that FoxG1 can function as a pro-apoptotic factor in part through suppression of AIB1 coactivator transcription complex formation, thereby reducing the expression of the AIB1 oncogene.

[133]

**TÍTULO / TITLE:** - A preliminary algorithm introducing immunogenicity assessment in the management of patients with RA receiving tumour necrosis factor inhibitor therapies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Rheum Dis. 2013 May 11.

●●Enlace al texto completo (gratis o de pago) [1136/annrheumdis-2013-203296](#)

**AUTORES / AUTHORS:** - Garces S; Antunes M; Benito-Garcia E; da Silva JC; Aarden L; Demengeot J

**INSTITUCIÓN / INSTITUTION:** - Department of Immunology, Instituto Gulbenkian de Ciencia, Oeiras, Portugal.

**RESUMEN / SUMMARY:** - INTRODUCTION: Clinical remission is today the treatment goal for rheumatoid arthritis (RA), which requires fast and assertive therapeutic decisions for a tight control of disease activity. Few objective parameters are available to guide clinical decisions, particularly in switcher patients. We designed a preliminary algorithm introducing immunogenicity assessment in the current approach to patients with RA receiving tumour necrosis factor inhibitors (TNFi). OBJECTIVE: To evaluate the concordance between the new algorithm and current clinical practice, comparing the effectiveness of 'immunogenicity-based' versus 'empirical-based' switches in a cohort of patients with established RA receiving biologics. METHODS: EULAR therapeutic response was evaluated in 105 patients with RA (naive or switchers) over one year, through generalised estimation equation (GEE) analyses. Serum drug trough levels were assessed by ELISA and antidrug antibodies (ADAb) by Bridging ELISA. RESULTS: During follow-up, 48.6% of patients had therapeutic decisions concordant with the proposed algorithm (Group A), and 51.4% had discordant decisions (Group B). One year after the therapeutic decision, patients from Group A had a higher probability of achieving response (OR=7.91, p<0.001, 95% CI 3.27 to 19.13) and low disease activity (OR=9.77, p<0.001, 95% CI 4.69 to 20.37) than patients in Group B. CONCLUSIONS: Immunogenicity assessment might help to optimise

therapeutic decisions, leading to a better control of disease activity with significantly better clinical outcomes in patients with RA receiving TNFi.

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[134]

**TÍTULO / TITLE:** - Human Vgamma2Vdelta2 T cells limit breast cancer growth by modulating cell survival-, apoptosis-related molecules and microenvironment in tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Apr 18. doi: 10.1002/ijc.28217.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28217](#)

**AUTORES / AUTHORS:** - Aggarwal R; Lu J; Kanji S; Das M; Joseph M; Lustberg MB; Ray A; Pompili VJ; Shapiro CL; Das H

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Wexner Medical Center at The Ohio State University, Columbus, OH.

**RESUMEN / SUMMARY:** - Innate immune system has been known to play an important role in inhibiting the malignant transformation, tumor progression and invasion. However, the mechanistic basis remains ambiguous. Despite polyclonality of human gammadelta T cells, Vgamma2Vdelta2 T cell subset was shown to recognize and limit the growth of various tumors at various degrees. The differential recognition of the tumor cells by Vgamma2Vdelta2 T cells are yet to be defined. Our study reveals that gammadelta T cells limit in vitro growth of most breast tumor cells, such as SkBr7 (HER2+), MCF7 (ER+) and MDA-MB-231 (ER-) by inhibiting their survival and inducing apoptosis, except BrCa-MZ01 (PR+) cells. To investigate detail mechanisms of antineoplastic effects, we found that cell death was associated with the surface expression levels of MICA/B and ICAM1. Molecular signaling analysis demonstrated that inhibition of cell growth by gammadelta T cells was associated with the lower expression levels of cell survival-related molecules such as AKT, ERK and concomitant upregulation of apoptosis-related molecules, such as PARP, cleaved caspase 3 and tumor suppressor genes PTEN and P53. However, opposite molecular signaling was observed in the resistant cell line after coculture with gammadelta T cells. In vivo, antineoplastic effects of gammadelta T cells were also documented, where tumor growth was inhibited due to the downregulation of survival signals, strong induction of apoptotic molecules, disruption of microvasculature and increased infiltration of tumor associated macrophages. These findings reveal that a complex molecular signaling is involved in gammadelta T cell-mediated antineoplastic effects.

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[135]

**TÍTULO / TITLE:** - Genetic polymorphism at Val (rs700518) of the CYP19A1 gene is associated with aromatase inhibitor associated bone loss in women with ER (+) breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bone. 2013 May 1;55(2):309-314. doi: 10.1016/j.bone.2013.04.021.

●●Enlace al texto completo (gratis o de pago) [1016/j.bone.2013.04.021](#)

**AUTORES / AUTHORS:** - Napoli N; Rastelli A; Ma C; Yarramaneni J; Vattikutti S; Moskowitz G; Giri T; Mueller C; Kulkarny V; Qualls C; Ellis M; Armamento-Villareal R

**INSTITUCIÓN / INSTITUTION:** - Washington University School of Medicine, St. Louis, MO, USA; Universita' Campus Bio-Medico, Rome, Italy.

**RESUMEN / SUMMARY:** - **PURPOSE:** Polymorphisms in the CYP19A1 (aromatase) gene have been reported to influence disease-free survival and the incidence of musculoskeletal complaints in patients taking aromatase inhibitors (AIs) for estrogen receptor positive (ER+) breast cancer. Bone loss and fractures are well-recognized complications from AI therapy. The objective of this study is to determine the influence of polymorphisms in the CYP19A1 gene on bone loss among patients taking aromatase inhibitors for ER+ breast cancer. **PATIENTS AND METHODS:** The subjects consisted of 97 postmenopausal women with ER+ breast cancer who were initiated on third-generation AIs. Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry at baseline and at 6 and 12 months. Twenty-four hour urine N-telopeptide (NTX) was measured by Elisa and serum estradiol was measured by ultrasensitive radioimmunoassay at baseline, and at 6 months. Genotyping was done by Taqman SNP allelic discrimination assay. **RESULTS:** Women with the AA genotype for the rs700518 (G/A at Val80) developed significant bone loss at the lumbar spine and the total hip at 12 months relative to patients carrying the G allele (GA/GG); both  $p=0.03$ . There was a borderline greater increase in urinary NTX in those with the AA genotype compared to patients with the G allele,  $p=0.05$ ; but no significant difference in changes in estradiol levels among the genotypes. **CONCLUSION:** Patients with the AA genotype for the rs700518 polymorphism in the CYP19A1 gene are at risk for AI-associated bone loss and deserve close follow-up during long-term AI therapy.

[136]

**TÍTULO / TITLE:** - Higher WHO grades of follicular lymphoma correlate with better outcome in two Nordic Lymphoma Group trials of rituximab without chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 12.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.802778](#)

**AUTORES / AUTHORS:** - Wahlin BE; Sundstrom C; Sander B; Christensson B; Jeppsson-Ahlberg A; Hjalmarsson E; Holte H; Ostenstad B; Brown PD; Smeland EB; Kimby E

**RESUMEN / SUMMARY:** - ABSTRACT A common treatment for follicular lymphoma is rituximab monotherapy. To identify patients for whom this regimen is adequate as first-line therapy, we applied the World Health Organization (WHO) classification for grading follicular lymphoma in a prospective central pathology review of the biopsies of previously untreated patients in two randomized trials of rituximab without chemotherapy. In the first trial (N1=53), higher WHO grades correlated with longer time to next treatment, independently of clinical prognostic factors ( $p=0.030$ ); the finding was replicated in the second trial (N2=221;  $p=0.019$ ). Higher grades were associated with better treatment responses ( $p=0.018$ ). Furthermore, also grades externally confirmed by independent local pathologists correlated with time to next treatment ( $p=0.048$ ). Flow cytometry in a separate patient series showed that the intensity of CD20 increased with the malignant cells' size ( $p<0.00005$ ). In conclusion, WHO grade 1 follicular lymphoma correlates with inferior outcome after rituximab monotherapy. WHO grading might provide a clinically useful tool for personalized therapy.

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[137]

**TÍTULO / TITLE:** - Acquired Resistance to EGFR Inhibitors Is Associated with a Manifestation of Stem Cell-like Properties in Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 May 15;73(10):3051-61. doi: 10.1158/0008-5472.CAN-12-4136. Epub 2013 Mar 29.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-4136](#)

**AUTORES / AUTHORS:** - Shien K; Toyooka S; Yamamoto H; Soh J; Jida M; Thu KL; Hashida S; Maki Y; Ichihara E; Asano H; Tsukuda K; Takigawa N; Kiura K; Gazdar AF; Lam WL; Miyoshi S

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Thoracic Surgery and Respiratory Medicine, Okayama University Hospital; Department of General Internal Medicine 4, Kawasaki Medical School, Okayama, Japan; Department of Integrative Oncology, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada; and Hamon Center for Therapeutic Oncology Research and Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas.

**RESUMEN / SUMMARY:** - Acquired resistance to EGF receptor (EGFR) tyrosine kinase inhibitor (TKI) is a critical problem in the treatment of lung cancer. Although several mechanisms have been shown to be responsible for acquired resistance, all mechanisms have not been uncovered. In this study, we investigated the molecular and cellular profiles of the acquired resistant cells to

EGFR-TKI in EGFR-mutant lung cancers. Four EGFR-mutant cell lines were exposed to gefitinib by stepwise escalation and high-concentration exposure methods, and resistant sublines to gefitinib were established. The molecular profiles and cellular phenotypes of these resistant sublines were characterized. Although previously reported, alterations including secondary EGFR T790M mutation, MET amplification, and appearance of epithelial-to-mesenchymal transition (EMT) features were observed, these 2 drug-exposure methods revealed different resistance mechanisms. The resistant cells with EMT features exhibited downregulation of miRNA-200c by DNA methylation. Furthermore, the HCC827-derived subline characterized by the high-concentration exposure method exhibited not only EMT features but also stem cell-like properties, including aldehyde dehydrogenase isoform 1 (ALDH1A1) overexpression, increase of side-population, and self-renewal capability. Resistant sublines with stem cell-like properties were resistant to conventional chemotherapeutic agents but equally sensitive to histone deacetylase and proteasome inhibitors, compared with their parental cells. ALDH1A1 was upregulated in clinical samples with acquired resistance to gefitinib. In conclusion, our study indicates that the manner of EGFR-TKI exposure influences the mechanism of acquired resistance and the appearance of stem cell-like property with EGFR-TKI treatment. Cancer Res; 73(10); 3051-61. ©2013 AACR.

[138]

**TÍTULO / TITLE:** - MYC protein expression and genetic alterations have prognostic impact in diffuse large B-cell lymphoma treated with immunochemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 May 28.

●●Enlace al texto completo (gratis o de pago)

[3324/haematol.2013.086173](http://3324/haematol.2013.086173)

**AUTORES / AUTHORS:** - Valera A; Lopez-Guillermo A; Cardesa-Salzman T; Climent F; Gonzalez-Barca E; Mercadal S; Espinosa I; Novelli S; Briones J; Mate JL; Salamero O; Sancho JM; Arenillas L; Serrano S; Erill N; Martinez D; Castillo P; Rovira J; Martinez A; Campo E; Colomo L

**INSTITUCIÓN / INSTITUTION:** - España;

**RESUMEN / SUMMARY:** - MYC alterations influence the survival of patients with diffuse large B-cell lymphoma. Most studies have focused on MYC translocations but there is little information regarding the impact of numerical alterations and protein expression. We analyzed the genetic alterations and protein expression of MYC, BCL2, BCL6, and MALT1 in 219 diffuse large B-cell lymphomas. MYC rearrangement occurred as the sole abnormality (MYC single-hit) in 3% of cases, MYC and concurrent BCL2 and/or BCL6 rearrangements (MYC double/triple-hit) in 4%, MYC amplifications in 2% and MYC gains in 19%. MYC single-hit, MYC double/triple-hit and MYC

amplifications, but not MYC gains or other gene rearrangements, were associated with unfavorable progression free survival and overall survival. MYC protein expression, evaluated using a computerized image analysis, captured the unfavorable prognosis of MYC translocations/amplifications and identified an additional subset of patients without gene alterations but with similar poor prognosis. Tumors expressing both MYC/BCL2 had the worst prognosis, whereas double negative tumors had the best outcome. High MYC expression was associated with shorter overall survival irrespective of the International Prognostic Index and BCL2 expression. In conclusion, MYC protein expression identifies a subset of diffuse large B-cell lymphoma with very poor prognosis independently of gene alterations and other prognostic parameters.

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[139]

**TÍTULO / TITLE:** - HOX antisense lincRNA HOXA-AS2 is an apoptosis repressor in all trans retinoic acid treated NB4 promyelocytic leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 May 3. doi: 10.1002/jcb.24586.

●●Enlace al texto completo (gratis o de pago) [1002/jcb.24586](#)

**AUTORES / AUTHORS:** - Zhao H; Zhang X; Frazao JB; Condino-Neto A; Newburger PE

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, University of Massachusetts Medical School, Worcester, MA, USA.

**RESUMEN / SUMMARY:** - HOXA cluster antisense RNA 2 (HOXA-AS2) is a long non-coding RNA located between the HOXA3 and HOXA4 genes in the HOXA cluster. Its transcript is expressed in NB4 promyelocytic leukemia cells and human peripheral blood neutrophils, and expression is increased in NB4 cells treated with all trans retinoic acid (ATRA). Knockdown of HOXA-AS2 expression by transduced shRNA decreases the number of viable cells and increases the proportion of apoptotic cells, measured by annexin V binding and by activity and cleavage of caspases-3, -8, and -9. The increase in death of HOXA-AS2 knockdown cells was accompanied by an elevated TNF-related apoptosis-inducing ligand (TRAIL) levels, but ATRA-induced NB4 cells treated with TRAIL did show an increase in HOXA-AS2 expression. These results demonstrate that ATRA induction of HOXA-AS2 suppresses ATRA-induced apoptosis, possibly through a TRAIL-mediated pathway. HOXA-AS2-mediated negative regulation thus contributes to the fine-tuning of apoptosis during ATRA-induced myeloid differentiation in NB4 cells. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

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[140]

**TÍTULO / TITLE:** - 18F-Fluorothymidine PET Is a Potential Predictive Imaging Biomarker of the Response to Gemcitabine-Based Chemotherapeutic Treatment for Recurrent Ovarian Cancer: Preliminary Results in Three Patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Nucl Med. 2013 May 1.

●●Enlace al texto completo (gratis o de pago)

[1097/RLU.0b013e318292ee9c](#)

**AUTORES / AUTHORS:** - Tsuyoshi H; Morishita F; Orisaka M; Okazawa H; Yoshida Y

**INSTITUCIÓN / INSTITUTION:** - From the \*Department of Obstetrics and Gynecology, Faculty of Medical Sciences, and daggerBiomedical Imaging Research Center, University of Fukui, Fukui, Japan.

**RESUMEN / SUMMARY:** - In order to establish early and precise methods for evaluating the effect of secondary chemotherapy in patients with recurrent ovarian cancer, both the clinical course of 3 women treated with gemcitabine-based secondary chemotherapy and the potential for early and accurate evaluation of the secondary chemotherapeutic effect of F-fluorothymidine (FLT) PET are reported. Standard uptake value with FLT PET decreased earlier than with F-fluorodeoxyglucose PET and was better correlated with a reduction in size as measured by CT. FLT PET could become a new standard for monitoring response to gemcitabine-based secondary chemotherapy treatment for recurrent ovarian cancer.

[141]

**TÍTULO / TITLE:** - Expression of group IIA phospholipase A2 is an independent predictor of favorable outcome for patients with gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Pathol. 2013 May 10. pii: S0046-8177(13)00117-2. doi: 10.1016/j.humpath.2013.01.027.

●●Enlace al texto completo (gratis o de pago)

[1016/j.humpath.2013.01.027](#)

**AUTORES / AUTHORS:** - Wang X; Huang CJ; Yu GZ; Wang JJ; Wang R; Li YM; Wu Q

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Changzheng Hospital, Second Military Medical University, Shanghai 200070, China.

**RESUMEN / SUMMARY:** - Growing evidence suggests that phospholipase A2 (PLA2) plays a pivotal role in tumorigenesis in human gastrointestinal cancer. One of the well-studied isoforms of PLA2, group IIA PLA2 (PLA2G2A), appears to exert its protumorigenic or antitumorigenic effects in a tissue-specific manner. The present study was designed to determine the expression profile and prognostic value of PLA2G2A in gastric cancer in a large Chinese cohort. By using real-time polymerase chain reaction, the amount of PLA2G2A messenger RNA in 60 pairs of fresh gastric tumors and adjacent noncancerous mucosa

was measured. The immunostaining of PLA2G2A in 866 gastric cancers with paired noncancerous tissues was assayed. No expression of PLA2G2A was found in normal gastric mucosa, and focal expression of PLA2G2A was noticed in intestinal metaplasia, whereas significantly increased expression of PLA2G2A was observed in the cytoplasm of gastric cancer cells. Furthermore, the extent of PLA2G2A expression was associated with tumor size ( $P < .001$ ), tumor differentiation ( $P = .001$ ), T class ( $P < .001$ ), N class ( $P < .001$ ), and TNM stage ( $P < .001$ ) of gastric cancer. Multivariate analysis showed that PLA2G2A expression was an independent predictor of survival for patients with gastric cancer ( $P = .024$ ). Expression of PLA2G2A seems to be protective for patients with gastric cancer (hazard ratio, 1.423; 95% confidence interval, 1.047-1.935), and it may be a target for achieving better treatment outcomes.

[142]

**TÍTULO / TITLE:** - Identification of Molecular Subtypes of Gastric Cancer with Different Responses to PI3-Kinase Inhibitors and 5-Fluorouracil.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gastroenterology. 2013 May 14. pii: S0016-5085(13)00722-1. doi: 10.1053/j.gastro.2013.05.010.

●●Enlace al texto completo (gratis o de pago)

[1053/j.gastro.2013.05.010](http://1053/j.gastro.2013.05.010)

**AUTORES / AUTHORS:** - Lei Z; Tan IB; Das K; Deng N; Zouridis H; Pattison S; Chua C; Feng Z; Guan YK; Ooi CH; Ivanova T; Zhang S; Lee M; Wu J; Ngo A; Manesh S; Tan E; Teh BT; Yan So JB; Goh LK; Boussioutas A; Hon Lim TK; Flotow H; Tan P; Rozen SG

**INSTITUCIÓN / INSTITUTION:** - Centre for Computational Biology; Cancer and Stem Cell Biology Program Duke-NUS Graduate Medical School, Singapore, 169857, Singapore.

**RESUMEN / SUMMARY:** - BACKGROUND: & Aims: Almost all gastric cancers are adenocarcinomas, which have considerable heterogeneity among patients. We sought to identify subtypes of gastric adenocarcinomas with particular biological properties and responses to chemotherapy and targeted agents. METHODS: We compared gene expression patterns among 248 gastric tumors; using a robust method of unsupervised clustering, consensus hierarchical clustering with iterative feature selection, we identified 3 major subtypes. We developed a classifier for these subtypes and validated it in 70 tumors from a different population. We identified distinct genomic and epigenomic properties of the subtypes. We determined drug sensitivities of the subtypes in primary tumors using clinical survival data, and of cell lines through high-throughput drug screening. RESULTS: We identified 3 subtypes of gastric adenocarcinoma, called proliferative, metabolic, and mesenchymal. Tumors of the proliferative subtype had high levels of genomic instability, TP53 mutations, and DNA hypomethylation. Cancer cells of the metabolic subtype were more sensitive to

5-fluorouracil than the other subtypes. Furthermore, in 2 independent groups of patients, those with tumors of the metabolic subtype appeared to have greater benefits from 5-fluorouracil treatment. Tumors of the mesenchymal subtype contain cells with features of cancer stem cells, and cell lines of this subtype are particularly sensitive to PI3K-AKT-mTOR inhibitors in vitro. CONCLUSIONS: Based on gene expression patterns, we classified gastric cancers into 3 subtypes, and validated these in an independent set of tumors. The subgroups have differences in molecular and genetic features and response to therapy; this information might be used to select specific treatment approaches for patients with gastric cancer.

[143]

**TÍTULO / TITLE:** - Interleukin-2-induced Graft-Versus-Leukemia for the Treatment of AML in a BRCA2 Fanconi Anemia Patient.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pediatr Hematol Oncol. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago)

[1097/MPH.0b013e31828e5c56](#)

**AUTORES / AUTHORS:** - Yeo CJ; Gilman AL

**INSTITUCIÓN / INSTITUTION:** - \*School of Clinical Medicine, University of Cambridge, Cambridge, UK daggerDivision of Blood and Marrow Transplantation, Levine Children's Hospital, Charlotte, NC.

**RESUMEN / SUMMARY:** - Biallelic BRCA2 mutations occur in 2% of patients with Fanconi anemia and are associated with a high risk of acute leukemia at an early age and a poor prognosis. For the first time, we report the use of interleukin-2 to stimulate a graft-versus-leukemia effect and induce complete remission in a patient with BRCA2 Fanconi anemia and refractory acute myelogenous leukemia, suggesting the potential of immunotherapy in this setting. Interleukin-2 was associated with significant infusion-related toxicity.

[144]

**TÍTULO / TITLE:** - Influence of pretreatment ideal body weight percentile and albumin on the prognosis of nasopharyngeal carcinoma: Long-term outcomes of 512 patients from a single institution.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Head Neck. 2013 Apr 22. doi: 10.1002/hed.23357.

●●Enlace al texto completo (gratis o de pago) [1002/hed.23357](#)

**AUTORES / AUTHORS:** - Li G; Gao J; Liu ZG; Tao YL; Xu BQ; Tu ZW; Zhang XP; Zeng MS; Xia YF

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in Southern China, Sun Yat-Sen University, Guangzhou, People's Republic of China; Department of Radiation Oncology, Sun Yat-sen University Cancer Center,

Guangzhou, People's Republic of China; Department of Radiation Oncology, Guangzhou Medical University Cancer Institute and Hospital, Guangzhou, People's Republic of China.

**RESUMEN / SUMMARY:** - Background: This study was to investigate the relationship between pretreatment nutritional status and prognosis of nasopharyngeal carcinoma (NPC). Methods: Pretreatment nutritional status was evaluated by ideal body weight percentile (IBW %) and serum albumin for 512 NPC patients received radical radiotherapy. Kaplan-Meier methods, log-rank test, and a Cox model were applied for survival analysis. Results: Before radiotherapy, IBW% < 90% was related to poorer overall survival (OS) and distant metastasis free survival (DMFS) (P=0.031, P = 0.012); albumin <= 43.0 g/ L was related to poorer OS and DMFS (P < 0.001, P = 0.042); both IBW% and albumin were independent prognostic factors for OS; those patients with IBW% < 90% and albumin <= 43.0 g/ L simultaneously had the worst OS and DMFS. Conclusions: Decrease of pretreatment IBW% and albumin was related to poorer survival of NPC. Head Neck, 2013.

[145]

**TÍTULO / TITLE:** - ERCC1/BRCA1 expression and gene polymorphisms as prognostic and predictive factors in advanced NSCLC treated with or without cisplatin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Apr 30;108(8):1695-703. doi: 10.1038/bjc.2013.127. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.127](http://1038/bjc.2013.127)

**AUTORES / AUTHORS:** - Tiseo M; Bordi P; Bortesi B; Boni L; Boni C; Baldini E; Grossi F; Recchia F; Zanelli F; Fontanini G; Naldi N; Campanini N; Azzoni C; Bordi C; Ardizzoni A

**INSTITUCIÓN / INSTITUTION:** - Oncology Unit, University Hospital, Via Gramsci 14, 43126 Parma, Italy.

**RESUMEN / SUMMARY:** - Background: The FAST was a factorial trial in first-line treatment of advanced non-small-cell lung cancer (NSCLC), addressing the role of replacing cisplatin with a non-platinum agent. The prognostic and predictive effect of ERCC1/BRCA1 expression and ERCC1/XPD/XRCC1-3 gene polymorphisms on outcomes of patients was examined. Methods: Patients were randomised to receive treatment with or without cisplatin. ERCC1/BRCA1 expression was determined by immunohistochemistry. ERCC1 (C8092A, C118T), XPD (Lys751Gln), XRCC1 (Arg399Gln) and XRCC3 (Thr241Met) gene polymorphisms were evaluated on tumour DNA by TaqMan allelic discrimination assay. Results: Tumour samples were available from 110 of 433 patients enrolled: 54.7% were ERCC1 positive and 51.4% were BRCA1 positive. Overall, ERCC1-negative patients had better response rate (P=0.004), progression-free survival (P=0.023) and overall survival (P=0.012) compared

with positive ones, with no statistically significant treatment interaction. The BRCA1-positive patients showed numerically better outcomes, although not statistically significant, with no treatment interaction. Among DNA repair gene polymorphisms, only XRCC1 Gln/Gln genotype evidenced a potential prognostic role (P=0.036). Conclusion: This study confirms the prognostic role of ERCC1 expression and XRCC1 (Arg399Gln) polymorphism in advanced NSCLC treated with first-line chemotherapy. None of these biomarkers was shown to be a specific predictive factor of cisplatin efficacy.

[146]

**TÍTULO / TITLE:** - Prediction of Response to Anticancer Immunotherapy Using Gene Signatures.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2013.49.2157](#)

**AUTORES / AUTHORS:** - Wang E; Bedognetti D; Marincola FM

**INSTITUCIÓN / INSTITUTION:** - National Institutes of Health, Bethesda, MD.

[147]

**TÍTULO / TITLE:** - Predictive Gene Signature in MAGE-A3 Antigen-Specific Cancer Immunotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.44.3762](#)

**AUTORES / AUTHORS:** - Ulloa-Montoya F; Louahed J; Dizier B; Gruselle O; Spiessens B; Lehmann FF; Suciú S; Kruit WH; Eggermont AM; Vansteenkiste J; Brichard VG

**INSTITUCIÓN / INSTITUTION:** - Fernando Ulloa-Montoya, Jamila Louahed, Benjamin Dizier, Olivier Gruselle, Bart Spiessens, Frederic F. Lehmann, and Vincent G. Brichard, GlaxoSmithKline Vaccines, Rixensart; Stefan Suciú, European Organisation for Research and Treatment of Cancer Headquarters, Brussels; Johan Vansteenkiste, University Hospital Leuven/KU Leuven, Leuven, Belgium; Wim H.J. Kruit, Erasmus Medical Center, Rotterdam, the Netherlands; and Alexander M.M. Eggermont, Institut Gustave Roussy, Villejuif, France.

**RESUMEN / SUMMARY:** - PURPOSE To detect a pretreatment gene expression signature (GS) predictive of response to MAGE-A3 immunotherapeutic in patients with metastatic melanoma and to investigate its applicability in a different cancer setting (adjuvant therapy of resected early-stage non-small-cell lung cancer [NSCLC]). PATIENTS AND METHODS Patients were participants in two phase II studies of the recombinant MAGE-A3 antigen combined with an immunostimulant (AS15 or AS02B). mRNA from melanoma biopsies was analyzed by microarray analysis and quantitative polymerase chain reaction.

These results were used to identify and cross-validate the GS, which was then applied to the NSCLC data. Results In the patients with melanoma, 84 genes were identified whose expression was potentially associated with clinical benefit. This effect was strongest when the immunostimulant AS15 was included in the immunotherapy (hazard ratio [HR] for overall survival, 0.37; 95% CI, 0.13 to 1.05; P = .06) and was less strong with the other immunostimulant AS02B (HR, 0.84; 95% CI, 0.36 to 1.97; P = .70). The same GS was then used to predict the outcome for patients with resected NSCLC treated with MAGE-A3 plus AS02B; actively treated GS-positive patients showed a favorable disease-free interval compared with placebo-treated GS-positive patients (HR, 0.42; 95% CI, 0.17 to 1.03; P = .06), whereas among GS-negative patients, no such difference was found (HR, 1.17; 95% CI, 0.59 to 2.31; P = .65). The genes identified were mainly immune related, involving interferon gamma pathways and specific chemokines, suggesting that their pretreatment expression influences the tumor's immune microenvironment and the patient's clinical response. CONCLUSION An 84-gene GS associated with clinical response for MAGE-A3 immunotherapeutic was identified in metastatic melanoma and confirmed in resected NSCLC.

[148]

**TÍTULO / TITLE:** - Using early viral kinetics to predict antiviral outcome in response-guided pegylated interferon plus ribavirin therapy among patients with hepatitis C virus genotype 1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gastroenterol. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s00535-013-0824-](http://1007/s00535-013-0824-)

[Z](#)

**AUTORES / AUTHORS:** - Oze T; Hiramatsu N; Yakushijin T; Miyazaki M; Iio S; Oshita M; Hagiwara H; Mita E; Inui Y; Hijioka T; Inada M; Tamura S; Yoshihara H; Inoue A; Imai Y; Miyagi T; Yoshida Y; Tatsumi T; Kanto T; Kasahara A; Hayashi N; Takehara T

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: HCV kinetics during treatment demonstrated strong association with the antiviral outcome of patients treated with pegylated interferon (Peg-IFN) plus ribavirin. However, the relationship between HCV kinetics and pre-treatment factors remains unclear. METHODS: Of 547 patients with HCV genotype 1 treated with Peg-IFN alfa-2b plus ribavirin, 401 completed the response-guided therapy and were assessed for per protocol analysis. RESULTS: The sustained virologic response (SVR) rate was 53 % for all patients, 60 % for those with genotype TT, and 19 % for those with genotype TG/GG according to IL28B (rs8099917) single nucleotide

polymorphisms. The SVR rates increased with HCV decrease at week 4; 4 % (2/56) with <1 log<sub>10</sub> decrease, 13 % (7/56) with 1-2 log<sub>10</sub> decrease, 51 % (44/87) with 2-3 log<sub>10</sub> decrease, 64 % (56/87) with 3-4 log<sub>10</sub> decrease, 88 % (72/82) with more than 4 log<sub>10</sub> decrease but with detectable HCV RNA and 100 % (33/33) with undetectable HCV RNA (p < 0.001). Similarly, SVR rates increased step-by-step in proportion to HCV decrease in both IL28B TT and TG/GG groups, showing almost the same SVR rates for the same conditions. In multivariate analysis, age (p = 0.005) and the magnitude of HCV decrease at week 4 (p < 0.001) but not IL28B were associated with SVR. Advanced liver fibrosis (p = 0.004) and the magnitude of HCV decrease at week 4 (p < 0.001) but not IL28B were associated with non-response. CONCLUSIONS: The magnitude of the HCV decrease at week 4 seems to be the most reliable marker for predicting antiviral outcome after starting Peg-IFN plus ribavirin therapy.

[149]

**TÍTULO / TITLE:** - beta1 Integrin Targeting Potentiates Antiangiogenic Therapy and Inhibits the Growth of Bevacizumab-Resistant Glioblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 May 15;73(10):3145-54. doi: 10.1158/0008-5472.CAN-13-0011. Epub 2013 May 3.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-0011](http://1158/0008-5472.CAN-13-0011)

**AUTORES / AUTHORS:** - Carbonell WS; Delay M; Jahangiri A; Park CC; Aghi MK

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Neurosurgery and Radiation Oncology, University of California, San Francisco, San Francisco, California.

**RESUMEN / SUMMARY:** - Antiangiogenic therapies like bevacizumab offer promise for cancer treatment, but acquired resistance, which often includes an aggressive mesenchymal phenotype, can limit the use of these agents. Upregulation of beta1 integrin (ITGB1) occurs in some bevacizumab-resistant glioblastomas (BRG) whereby, mediating tumor-microenvironment interactions, we hypothesized that it may mediate a mesenchymal-type resistance to antiangiogenic therapy. Immunostaining analyses of beta1 integrin and its downstream effector kinase FAK revealed upregulation in 75% and 86% of BRGs, respectively, compared with pretreatment paired specimens. Furthermore, flow cytometry revealed eight-fold more beta1 integrin in primary BRG cells compared with cells from bevacizumab-naive glioblastomas (BNG). Fluorescence recovery after photobleaching of cells engineered to express a beta1-GFP fusion protein indicated that the mobile beta1 integrin fraction was doubled, and half-life of beta1 integrin turnover in focal adhesions was reduced markedly in BRG cells compared with bevacizumab-responsive glioblastoma multiforme cells. Hypoxia, which was increased with acquisition of bevacizumab

resistance, was associated with increased beta1 integrin expression in cultured BNG cells. BRGs displayed an aggressive mesenchymal-like phenotype in vitro. We found that growth of BRG xenograft tumors was attenuated by the beta1 antibody, OS2966, allowing a 20-fold dose reduction of bevacizumab per cycle in this model. Intracranial delivery of OS2966 through osmotic pumps over 28 days increased tumor cell apoptosis, decreased tumor cell invasiveness, and blunted the mesenchymal morphology of tumor cells. We concluded that beta1 integrin upregulation in BRGs likely reflects an onset of hypoxia caused by antiangiogenic therapy, and that beta1 inhibition is well tolerated in vivo as a tractable strategy to disrupt resistance to this therapy. Cancer Res; 73(10); 3145-54. ©2013 AACR.

[150]

**TÍTULO / TITLE:** - Prognostic Significance of Pretreatment F-FDG PET/CT in Patients with Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma Treated by Radioimmunotherapy Using I-Rituximab.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Haematol. 2013 Mar 20;130(2):74-82.

●●Enlace al texto completo (gratis o de pago) [1159/000346436](#)

**AUTORES / AUTHORS:** - Lim I; Park JY; Kang HJ; Hwang JP; Lee SS; Kim KM; Choi TH; Yang SH; Kim BI; Choi CW; Lim SM

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, Korea Cancer Center Hospital, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - Aims: It was the aim of this paper to identify prognostic factors in patients with relapsed or refractory B-cell non-Hodgkin's lymphomas, treated by radioimmunotherapy (RIT) with radioiodinated human/murine chimeric anti-CD20 monoclonal antibody rituximab (131I-rituximab). Methods: Twenty-four patients were enrolled prospectively and were treated with unlabeled rituximab 70 mg and a therapeutic activity (median 7.3 GBq) of 131I-rituximab. Contrast-enhanced 18F-FDG PET/CT scans were performed before and after 1 month of RIT. Tumor sizes and maximum standardized uptake values (SUVmax) of scans were measured. Results: Four of the 24 patients survived. High SUVmax in a pretreatment scan was found to be related to poorer overall survival (OS) and progression-free survival ( $p = 0.04$  and  $0.02$ , respectively). Furthermore, a large tumor size in a pretreatment scan was associated with poorer OS but not with progression-free survival ( $p < 0.01$  and  $p = 0.07$ , respectively). By multivariate analyses, a high SUVmax, a large tumor size in a pretreatment scan and diffuse large B-cell lymphoma histology were significantly associated with poorer OS [ $p = 0.04$ /hazard ratio (HR) = 3.54,  $p < 0.01$ /HR = 5.52, and  $p = 0.02$ /HR = 3.38, respectively). Conclusion: SUVmax and tumor size determined by a pretreatment 18F-FDG PET/CT result as significant predictors of OS in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma treated by RIT.

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[151]

**TÍTULO / TITLE:** - Outcomes in Patients With Mixed Phenotype Acute Leukemia in Morocco.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pediatr Hematol Oncol. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago)

[1097/MPH.0b013e31828e54a5](#)

**AUTORES / AUTHORS:** - Bachir F; Zerrouk J; Howard SC; Graoui O; Lahjouji A; Hessissen L; Bennani S; Quessar A; El Aouad R

**INSTITUCIÓN / INSTITUTION:** - \*Laboratoire de cytometrie en flux, Institut National d'Hygiene daggerUnite d'hemato-oncologie pediatrique (UHOP), Hopital d'enfants, Rabat, Maroc double daggerService d'hematologie et oncologie pediatrique, Hopital, Casablanca, Maroc section signDepartment of Oncology, St. Jude Children's Research Hospital, Memphis, TN.

**RESUMEN / SUMMARY:** - Mixed phenotype acute leukemia (MPAL) includes biphenotypic and bilineal types of leukemia, which constitute rare subtypes that require individualized therapy. Outcomes in Moroccan patients with MPAL are unknown. Among 1264 patients with acute leukemia, 20 were classified as having MPAL, including 17 with biphenotypic acute leukemia (1.3%) and 3 with bilineal leukemia (0.2%). There were 8 adults and 12 children. In 12 cases (60%), leukemic blasts expressed myeloid and T-lymphoid antigens, and, in 5 cases (25%), leukemic blasts expressed B lymphoid antigens plus myeloid antigens. Patients were initially treated on protocols for acute myeloid leukemia (n=4), acute lymphoblastic leukemia (ALL, n=14), or with palliative care (n=2). The probability of survival at 2 years in MPAL cases was 52%+/-14%. Six of the 12 patients younger than 15 years remain alive versus 1 of 8 adult patients. Patients treated with ALL-directed therapy had significantly higher overall survival than those treated with acute myeloid leukemia-directed therapy (P=0.003). There was no association between the phenotypic characteristics and the clinical outcome (P=0.83). In conclusion, MPAL represents 1.5% of acute leukemia in Morocco. The prognosis is poor, but initial treatment with therapy directed toward ALL, improved supportive care, and the prevention of abandonment of therapy may improve outcomes in this subgroup of patients.

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[152]

**TÍTULO / TITLE:** - Elevation of Receptor Tyrosine Kinases by Small Molecule AKT Inhibitors in Prostate Cancer Is Mediated by Pim-1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 Jun 1;73(11):3402-11. doi: 10.1158/0008-5472.CAN-12-4619. Epub 2013 Apr 12.

●●Enlace al texto completo (gratuito o de pago) [1158/0008-5472.CAN-12-4619](https://doi.org/10.1158/0008-5472.CAN-12-4619)

**AUTORES / AUTHORS:** - Cen B; Mahajan S; Wang W; Kraft AS

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Medicine; and The Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina.

**RESUMEN / SUMMARY:** - The PI3K/AKT pathway is hyperactivated in prostate cancer but its effective therapeutic targeting has proven difficult. In particular, the antitumor activity of AKT inhibitors is attenuated by upregulation of receptor tyrosine kinases (RTK) through an uncharacterized feedback mechanism. In this report, we show that RNA interference-mediated silencing or pharmacologic inhibition of Pim-1 activity curtails AKT inhibitor-induced upregulation of RTKs in prostate cancer cells. Although Pim kinases have been implicated in cap-dependent translational control, we find that in the context of AKT inhibition, the expression of RTKs is controlled by Pim-1 in a cap-independent manner by controlling internal ribosome entry. Combination of Pim and AKT inhibitors resulted in synergistic inhibition of prostate tumor growth in vitro and in vivo. Together, our results show that Pim-1 mediates resistance to AKT inhibition and suggest its targeting to improve the efficacy of AKT inhibitors in anticancer therapy. Cancer Res; 73(11); 3402-11. ©2013 AACR.

[153]

**TÍTULO / TITLE:** - Genetic polymorphisms associated with oxaliplatin-induced peripheral neurotoxicity in Japanese patients with colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Pharmacol Ther. 2013 Jun;51(6):475-81. doi: 10.5414/CP201851.

●●Enlace al texto completo (gratuito o de pago) [5414/CP201851](https://doi.org/10.5414/CP201851)

**AUTORES / AUTHORS:** - Oguri T; Mitsuma A; Inada-Inoue M; Morita S; Shibata T; Shimokata T; Sugishita M; Nakayama G; Uehara K; Hasegawa Y; Ando Y

**RESUMEN / SUMMARY:** - Objective: Pharmacogenomic associations between severe oxaliplatin-induced chronic peripheral neurotoxicity (OXCPN) (Grade 2 lasting for > 7 days or Grade 3) and 9 single nucleotide polymorphisms (SNPs) in 8 genes (TAC1, FOXC1, ITGA1, ACYP2, DLEU7, BTG4, CAMK2N1, and FARS2) were reported by the genomewide association study (GWAS) in Korean patients. The present study was designed to explore reliable predictors of OXCPN and thereby improve the management of metastatic colorectal cancer (CRC). Methods: We retrospectively investigated pharmacogenomic characteristics of OXCPN in 70 Japanese patients with CRC who received oxaliplatin-based chemotherapy and updated the results of our previous analysis of ERCC1 (C118T, rs11615 and C8092A, rs3212986) and GSTP1 (Ile105Val, rs1695) polymorphisms. Results: Univariate analysis suggested potential associations of severe OXCPN with rs843748 in ACYP2 and

rs17140129 in FARS2, as well as with the absence of diabetes mellitus (DM) ( $p = 0.056, 0.072, \text{ and } 0.029$ , respectively). There was no association between severe OXCPN and any of the 7 other SNPs. Multiple logistic regression analysis showed that an increased risk of severe OXCPN was related to rs17140129 and the absence of DM ( $p = 0.034 \text{ and } 0.030$ , respectively). On updated analysis, polymorphisms of ERCC1 (C118T, rs11615) and rs10486003 in TAC1 were associated with time to the onset of Grade 1 OXCPN ( $p = 0.024 \text{ and } 0.049$ , respectively). Conclusions: Severe OXCPN is significantly related to rs17140129, found in the GWAS of Korean patients, in Japanese patients. Patients without DM are more likely to have OXCPN. The association between ERCC1 polymorphism and time to the onset of OXCPN was significant on updated analysis.

[154]

**TÍTULO / TITLE:** - Rotavirus-Encoded Nonstructural Protein 1 Modulates Cellular Apoptotic Machinery by Targeting Tumor Suppressor Protein p53.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Virol. 2013 Jun;87(12):6840-50. doi: 10.1128/JVI.00734-13. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1128/JVI.00734-13](#)

**AUTORES / AUTHORS:** - Bhowmick R; Halder UC; Chattopadhyay S; Nayak MK; Chawla-Sarkar M

**INSTITUCIÓN / INSTITUTION:** - Division of Virology, National Institute of Cholera and Enteric Diseases, Beliaghata, Kolkata, India.

**RESUMEN / SUMMARY:** - p53, a member of the innate immune system, is triggered under stress to induce cell growth arrest and apoptosis. Thus, p53 is an important target for viruses, as efficient infection depends on modulation of the host apoptotic machinery. This study focuses on how rotaviruses manipulate intricate p53 signaling for their advantage. Analysis of p53 expression revealed degradation of p53 during initial stages of rotavirus infection. However, in nonstructural protein-1 (NSP1) mutant strain A5-16, p53 degradation was not observed, suggesting a role of NSP1 in this process. This function of NSP1 was independent of its interferon or phosphatidylinositol 3-kinase (PI3K)/AKT modulation activity since p53 degradation was observed in Vero cells as well as in the presence of PI3K inhibitor. p53 transcript levels remained the same in SA11-infected cells (at 2 to 14 h postinfection), but p53 protein was stabilized only in the presence of MG132, suggesting a posttranslational process. NSP1 interacted with the DNA binding domain of p53, resulting in ubiquitination and proteasomal degradation of p53. Degradation of p53 during initial stages of infection inhibited apoptosis, as the proapoptotic genes PUMA and Bax were downregulated. During late viral infection, when progeny dissemination is the main objective, the NSP1-p53 interaction was diminished, resulting in restoration of the p53 level, with initiation of proapoptotic

signaling ensuing. Overall results highlight the multiple strategies evolved by NSP1 to combat the host immune response.

[155]

**TÍTULO / TITLE:** - Protein tyrosine phosphatase kappa (PTPRK) is a negative regulator of adhesion and invasion of breast cancer cells, and associates with poor prognosis of breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1007/s00432-013-1421-](#)

[5](#)

**AUTORES / AUTHORS:** - Sun PH; Ye L; Mason MD; Jiang WG

**INSTITUCIÓN / INSTITUTION:** - Metastasis and Angiogenesis Research Group, Institute of Cancer and Genetics, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK, [sunp2@cf.ac.uk](mailto:sunp2@cf.ac.uk).

**RESUMEN / SUMMARY:** - PURPOSE: Receptor-like protein tyrosine phosphatase kappa (PTPRK) has been shown to exhibit homophilic binding. It is a putative tumour suppressor in primary central nervous system lymphomas and colorectal cancer. The present study investigated the expression of PTPRK in breast cancer and the biological impact of PTPRK on breast cancer cells. METHODS: Expression of PTPRK protein and gene transcript was examined in a cohort of breast cancer patients. The association of PTPRK transcript level and pathological and clinical aspects was then analysed. Knockdown of PTPRK in breast cancer cells was performed using a specific anti-PTPRK transgene. The impact of PTPRK knockdown on breast cancer cells was investigated using in vitro cell function assays. RESULTS: Lower levels of PTPRK transcripts were seen in the advanced breast cancer. The reduced PTPRK transcript levels were associated with poor prognosis of the disease. PTPRK transcript levels were decreased in the primary tumours of patients who died from breast cancer or had metastases. Patients with lower expression of PTPRK had shorter survival compared with those higher expression levels of PTPRK. Knockdown of PTPRK resulted in increased proliferation, adhesion, invasion, and migration of breast cancer cells in vitro. CONCLUSIONS: Decreased expression of PTPRK in breast cancer is correlated with poor prognosis. PTPRK is a negative regulator of adhesion, invasion, migration, and proliferation of breast cancer cells. This suggests that PTPRK is a potential tumour suppressor in breast cancer.

[156]

**TÍTULO / TITLE:** - ASS1 as a Novel Tumor Suppressor Gene in Myxofibrosarcomas: Aberrant Loss via Epigenetic DNA Methylation Confers

Aggressive Phenotypes, Negative Prognostic Impact, and Therapeutic Relevance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Jun 1;19(11):2861-2872. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-2641](#)

**AUTORES / AUTHORS:** - Huang HY; Wu WR; Wang YH; Wang JW; Fang FM; Tsai JW; Li SH; Hung HC; Yu SC; Lan J; Shiue YL; Hsing CH; Chen LT; Li CF

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Pathology, Orthopedic Surgery, Radiation Oncology, and Division of Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine; Institute of Biomedical Science, National Sun Yat-Sen University; Department of Pathology, E-Da Hospital; Departments of Internal Medicine and Cancer Center and Pathology, Kaohsiung Medical University Hospital, and Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung; Institutes of Biosignal Transduction and Molecular Medicine, National Cheng Kung University; Departments of Anesthesiology and Pathology, Chi-Mei Medical Center; National Institute of Cancer Research, National Health Research Institutes; and Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan.

**RESUMEN / SUMMARY:** - **PURPOSE:** The principal goals were to identify and validate targetable metabolic drivers relevant to myxofibrosarcoma pathogenesis using a published transcriptome. **EXPERIMENTAL DESIGN:** As the most significantly downregulated gene regulating amino acid metabolism, argininosuccinate synthetase (ASS1) was selected for further analysis by methylation-specific PCR, pyrosequencing, and immunohistochemistry of myxofibrosarcoma samples. The roles of ASS1 in tumorigenesis and the therapeutic relevance of the arginine-depriving agent pegylated arginine deiminase (ADI-PEG20) were elucidated in ASS1-deficient myxofibrosarcoma cell lines and xenografts with and without stable ASS1 reexpression. **RESULTS:** ASS1 promoter hypermethylation was detected in myxofibrosarcoma samples and cell lines and was strongly linked to ASS1 protein deficiency. The latter correlated with increased tumor grade and stage and independently predicted a worse survival. ASS1-deficient cell lines were auxotrophic for arginine and susceptible to ADI-PEG20 treatment, with dose-dependent reductions in cell viability and tumor growth attributable to cell-cycle arrest in the S-phase. ASS1 expression was restored in 2 of 3 ASS1-deficient myxofibrosarcoma cell lines by 5-aza-2'-deoxycytidine, abrogating the inhibitory effect of ADI-PEG20. Conditioned media following ASS1 reexpression attenuated HUVEC tube-forming capability, which was associated with suppression of MMP-9 and an antiangiogenic effect in corresponding myxofibrosarcoma xenografts. In addition to delayed wound closure and fewer invading cells in a Matrigel assay, ASS1 reexpression reduced tumor cell proliferation, induced G1-phase arrest, and

downregulated cyclin E with corresponding growth inhibition in soft agar and xenograft assays. CONCLUSIONS: Our findings highlight ASS1 as a novel tumor suppressor in myxofibrosarcomas, with loss of expression linked to promoter methylation, clinical aggressiveness, and sensitivity to ADI-PEG20. Clin Cancer Res; 19(11); 2861-72. ©2013 AACR.

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[157]

**TÍTULO / TITLE:** - Dysregulation of BAG-1 in hepatocellular carcinoma predicts patient outcome and mediates increased resistance to doxorubicin-induced apoptosis via NF-kappaB pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 Apr 3. doi: 10.1002/jcb.24560.

●●Enlace al texto completo (gratis o de pago) [1002/jcb.24560](#)

**AUTORES / AUTHORS:** - Ni W; Chen B; Zhou G; Lu C; Xiao M; Guan C; Zhang Y; He S; Shen A; Ni R

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Affiliated Hospital of Nantong University, Nantong, 226001, P.R. China.

**RESUMEN / SUMMARY:** - Bcl-2-associated athanogene-1 (BAG-1) is a multifunctional anti-apoptotic protein which regulates an array of cellular processes, including apoptosis, signaling, proliferation, transcription, and cell motility and has been reported to be over-expressed in a number of human malignancies. To investigate the possible involvement of BAG-1 in tumorigenesis of hepatocellular carcinoma (HCC), we performed Western blot analysis in eight paired samples of HCC and adjacent peritumoral tissues and immunohistochemistry in 65 paraffin sections of HCC, which both showed an enhanced expression of nuclear BAG-1 isoform in HCC tissues. Statistical analysis confirmed that overexpression of nuclear BAG-1 in HCC tissues was significantly associated with histological grading ( $P < 0.001$ ), poor prognosis ( $P = 0.004$ ), and was found to be an independent prognostic indicator for HCC ( $P = 0.023$ ). We also noted that BAG-1 was overexpressed in four HCC cell lines compared with a normal hepatocyte cell line, and BAG-1 overexpression increased resistance of HCC cells to doxorubicin, a common chemotherapeutic agent for HCC. Furthermore, we observed that knock down of BAG-1 with siRNA in HepG2 cells increased the chemosensitivity of cells, a process mediated through inhibition of doxorubicin-triggered NF-kappaB activation; and knock down of BAG-1 suppressed proliferation and cell cycle transition of HepG2 cells. In consequence, our results for the first time indicated that BAG-1 was dysregulated in HCC and suppression of BAG-1 expression which resulted in inhibiting of NF-kappaB signaling might be developed into a new strategy in HCC therapy. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

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[158]

**TÍTULO / TITLE:** - Combination of Oxidative Stress and FOXM1 Inhibitors Induces Apoptosis in Cancer Cells and Inhibits Xenograft Tumor Growth.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Pathol. 2013 May 10. pii: S0002-9440(13)00269-1. doi: 10.1016/j.ajpath.2013.03.012.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ajpath.2013.03.012](#)

**AUTORES / AUTHORS:** - Halasi M; Pandit B; Wang M; Nogueira V; Hay N; Gartel AL

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, University of Illinois at Chicago, Chicago, Illinois.

**RESUMEN / SUMMARY:** - Tumor cells accumulate high level of reactive oxygen species (ROS) because they are metabolically more active than normal cells. Elevated ROS levels increase tumorigenicity but also render cancer cells more vulnerable to oxidative stress than normal cells. The oncogenic transcription factor Forkhead Box M1 (FOXM1), which is overexpressed in a wide range of human cancers, was reported to protect cancer cells from the adverse effects of oxidative stress by up regulating the expression of scavenger enzymes. We therefore hypothesized that the combination of FOXM1 ablation and ROS inducers could selectively eradicate cancer cells. We show that RNA interference-mediated knockdown of FOXM1 further elevates intracellular ROS levels and increases sensitivity of cancer cells to ROS-mediated cell death after treatment with ROS inducers. We also demonstrate that the combination of ROS inducers with FOXM1/proteasome inhibitors induces robust apoptosis in different human cancer cells. In addition, we show evidence that FOXM1/proteasome inhibitor bortezomib in combination with the ROS inducer beta-phenylethyl isothiocyanate efficiently inhibits the growth of breast tumor xenografts in nude mice. We conclude that the combination of ROS inducers and FOXM1 inhibitors could be used as a therapeutic strategy to selectively eliminate cancer cells.

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[159]

**TÍTULO / TITLE:** - MGMT promoter methylation status and prognosis of patients with primary or recurrent glioblastoma treated with carmustine wafers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Neurosurg. 2013 May 11.

●●Enlace al texto completo (gratis o de pago)

[3109/02688697.2013.791664](#)

**AUTORES / AUTHORS:** - Gutenberg A; Bock HC; Bruck W; Doerner L; Mehdorn HM; Roggendorf W; Westphal M; Felsberg J; Reifenberger G; Giese A

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Georg August University Göttingen, Göttingen, Germany.

**RESUMEN / SUMMARY:** - The prognostic role of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation in glioblastoma patients treated with carmustine (BCNU) wafer implantation is unclear. Here, we report on a retrospective study of 47 patients with either newly diagnosed (30 patients) or recurrent (17 patients) glioblastoma (WHO grade IV) treated with BCNU (bis-chloroethylnitrosourea) wafers. Thirteen of the newly diagnosed patients received local BCNU and irradiation only (first-line BCNU), while 17 patients additionally received concomitant and adjuvant temozolomide (TMZ) radiochemotherapy (first-line BCNU + TMZ). Of the 17 patients treated for recurrent glioblastoma (second-line BCNU), 16 had received radiotherapy with concomitant and adjuvant TMZ as an initial treatment. Median overall survival (OS) did not significantly differ between 19 patients with MGMT promoter methylated tumors when compared to 28 patients with unmethylated tumors (18.9 vs 15.0 months;  $p = 0.1054$ ). In the first-line BCNU + TMZ group, MGMT promoter methylation was associated with longer OS (21.0 vs 11.1 months,  $p = 0.0127$ ), while no significant survival differences were detected in the other two subgroups. Progression-free survival did not significantly differ between patients with and without MGMT promoter methylated tumors in the entire patient cohort or any of the three subgroups. The first-line BCNU + TMZ group showed no significant difference in OS when compared to the first-line BCNU group (18.9 vs 14.7 months), but tended to have more therapy-related adverse effects (53% vs 24%,  $p = 0.105$ ). In summary, MGMT promoter methylation showed a non-significant trend toward longer survival in our patient cohort. The combination of TMZ radiochemotherapy with local delivery of BCNU did not provide a significant survival benefit compared to local BCNU alone, but was associated with a higher rate of adverse effects. Owing to the small number of patients investigated, however, these findings would need to be corroborated in larger patient cohorts.

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[160]

**TÍTULO / TITLE:** - Insights from mixture cure modeling of molecular markers for prognosis in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Jun 1;31(16):2047-54. doi: 10.1200/JCO.2012.46.6615. Epub 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.46.6615](#)

**AUTORES / AUTHORS:** - Yilmaz YE; Lawless JF; Andrulis IL; Bull SB

**INSTITUCIÓN / INSTITUTION:** - Samuel Lunenfeld Research Institute of Mount Sinai Hospital, 60 Murray St, Box #18, Prosserman Centre for Health Research, Toronto, Ontario M5T 3L9 Canada; [bull@lunenfeld.ca](mailto:bull@lunenfeld.ca).

**RESUMEN / SUMMARY:** - With the ultimate aim of improving clinical management of breast cancer, investigators have sought to identify molecular genetic markers that stratify newly diagnosed patients into subtypes differing in short- or

long-term prognosis. Conventional survival models can fail to describe adequately the relationship between subtype and disease recurrence, particularly when there is a substantial proportion of long-term disease-free survivors. The observed patterns of disease-free survival in an undifferentiated patient cohort may be explained by an underlying mixture of two subgroups: patients who will remain free of disease in the long term (ie, cured), and those who will experience disease recurrence within their lifetime (ie, susceptible.) In this article, we review the concepts and methods of the mixture cure models and apply them in the analysis of molecular genetic prognostic factors for disease-free survival and time to disease recurrence in a cohort of patients with axillary lymph node-negative breast cancer.

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[161]

**TÍTULO / TITLE:** - Hyper-O-GlcNAcylation Is Anti-apoptotic and Maintains Constitutive NF-kappaB Activity in Pancreatic Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biol Chem. 2013 May 24;288(21):15121-30. doi: 10.1074/jbc.M113.470047. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1074/jbc.M113.470047](http://1074/jbc.M113.470047)

**AUTORES / AUTHORS:** - Ma Z; Vocadlo DJ; Vosseller K

**INSTITUCIÓN / INSTITUTION:** - From the Department of Biochemistry and Molecular Biology, Drexel University College of Medicine, Philadelphia, Pennsylvania 19102 and.

**RESUMEN / SUMMARY:** - Cancer cell metabolic reprogramming includes a shift in energy production from oxidative phosphorylation to less efficient glycolysis even in the presence of oxygen (Warburg effect) and use of glutamine for increased biosynthetic needs. This necessitates greatly increased glucose and glutamine uptake, both of which enter the hexosamine biosynthetic pathway (HBP). The HBP end product UDP-N-acetylglucosamine (UDP-GlcNAc) is used in enzymatic post-translational modification of many cytosolic and nuclear proteins by O-linked beta-N-acetylglucosamine (O-GlcNAc). Here, we observed increased HBP flux and hyper-O-GlcNAcylation in human pancreatic ductal adenocarcinoma (PDAC). PDAC hyper-O-GlcNAcylation was associated with elevation of OGT and reduction of the enzyme that removes O-GlcNAc (OGA). Reducing hyper-O-GlcNAcylation had no effect on non-transformed pancreatic epithelial cell growth, but inhibited PDAC cell proliferation, anchorage-independent growth, orthotopic tumor growth, and triggered apoptosis. PDAC is supported by oncogenic NF-kappaB transcriptional activity. The NF-kappaB p65 subunit and upstream kinases IKKalpha/IKKbeta were O-GlcNAcylated in PDAC. Reducing hyper-O-GlcNAcylation decreased PDAC cell p65 activating phosphorylation (S536), nuclear translocation, NF-kappaB transcriptional activity, and target gene expression. Conversely, mimicking PDAC hyper-O-GlcNAcylation through pharmacological inhibition of OGA suppressed

suspension culture-induced apoptosis and increased IKK $\alpha$  and p65 O-GlcNAcylation, accompanied by activation of NF- $\kappa$ B signaling. Finally, reducing p65 O-GlcNAcylation specifically by mutating two p65 O-GlcNAc sites (T322A and T352A) attenuated the induction of PDAC cell anchorage-independent growth. Our data indicate that hyper-O-GlcNAcylation is anti-apoptotic and contributes to NF- $\kappa$ B oncogenic activation in PDAC.

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[162]

**TÍTULO / TITLE:** - Nuclear localization of CPI-17, a protein phosphatase-1 inhibitor protein, affects histone H3 phosphorylation and corresponds to proliferation of cancer and smooth muscle cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Apr 26;434(1):137-42. doi: 10.1016/j.bbrc.2013.03.055. Epub 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.03.055](http://1016/j.bbrc.2013.03.055)

**AUTORES / AUTHORS:** - Eto M; Kirkbride JA; Chugh R; Karikari NK; Kim JI

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Physiology and Biophysics, and Kimmel Cancer Center, Thomas Jefferson University, 1020 Locust Street, PA 19107, USA. Electronic address: [masumi.eto@jefferson.edu](mailto:masumi.eto@jefferson.edu).

**RESUMEN / SUMMARY:** - CPI-17 (C-kinase-activated protein phosphatase-1 (PP1) inhibitor, 17kDa) is a cytoplasmic protein predominantly expressed in mature smooth muscle (SM) that regulates the myosin-associated PP1 holoenzyme (MLCP). Here, we show CPI-17 expression in proliferating cells, such as pancreatic cancer and hyperplastic SM cells. Immunofluorescence showed that CPI-17 was concentrated in nuclei of human pancreatic cancer (Panc1) cells. Nuclear accumulation of CPI-17 was also detected in the proliferating vascular SM cell culture and cells at neointima of rat vascular injury model. The N-terminal 21-residue tail domain of CPI-17 was necessary for the nuclear localization. Phospho-mimetic Asp-substitution of CPI-17 at Ser12 attenuated the nuclear import. CPI-17 phosphorylated at Ser12 was not localized at nuclei, suggesting a suppressive role of Ser12 phosphorylation in the nuclear import. Activated CPI-17 bound to all three isoforms of PP1 catalytic subunit in Panc1 nuclear extracts. CPI-17 knockdown in Panc1 resulted in dephosphorylation of histone H3 at Thr3, Ser10 and Thr11, whereas it had no effects on the phosphorylation of myosin light chain and merlin, the known targets of MLCP. In parallel, CPI-17 knockdown suppressed Panc1 proliferation. We propose that CPI-17 accumulated in the nucleus through the N-terminal tail targets multiple PP1 signaling pathways regulating cell proliferation.

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[163]

**TÍTULO / TITLE:** - Therapeutic enhancement of ER stress with Insulin Like Growth Factor 1 (IGF-1) sensitizes myeloma cells to proteasomal inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 14.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3134](#)

**AUTORES / AUTHORS:** - Tagoug I; Jordheim LP; Herveau S; Matera EL; Huber AL; Chettab A; Manie S; Dumontet C

**INSTITUCIÓN / INSTITUTION:** - Antibody anticancer, CRCL.

**RESUMEN / SUMMARY:** - PURPOSE: Multiple myeloma (MM) is a clonal plasma cell disorder in which growth and proliferation are linked to a variety of growth factors, including insulin-like growth factor type 1 (IGF-1). Bortezomib, the first-in-class proteasome inhibitor, has displayed significant antitumor activity in MM. EXPERIMENTAL DESIGN: We analyzed the impact of IGF-1 combined with proteasome inhibitors on MM cell lines in vivo and in vitro as well as on fresh human myeloma cells. RESULTS: Our study shows that IGF-1 enhances the cytotoxic effect of proteasome inhibitors against myeloma cells. The effect of bortezomib on the content of pro-apoptotic proteins such as Bax, Bad, Bak and Bim S and anti-apoptotic proteins such as Bcl-2, Bcl-XL, XIAP, Bfl-1 and survivin was enhanced by IGF-1. The addition of IGF-1 to bortezomib had minor effect on NF-kappaB signalling in MM.1S cells while strongly enhancing reticulum stress. This resulted in an unfolded protein response (UPR) which was required for the potentiating effect of IGF-1 on bortezomib cytotoxicity as shown by siRNA-mediated inhibition of GADD153 expression. CONCLUSIONS: These results suggest that the high baseline level of protein synthesis in myeloma can be exploited therapeutically by combining proteasome inhibitors with IGF-1, which possesses a "priming" effect on myeloma cells for this family of compounds.

[164]

**TÍTULO / TITLE:** - Transient and fully reversible leukocytosis in a myelodysplastic syndrome patient upon initiation of azacitidine treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 Apr 13.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1748-7](#)

**AUTORES / AUTHORS:** - Feldmann G; Brossart P; von Lilienfeld-Toal M

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine 3, Center of Integrated Oncology (CIO) Cologne-Bonn, University Hospital of Bonn, Sigmund-Freud-Str. 25, 53127, Bonn, Germany, [georg.feldmann@uni-bonn.de](mailto:georg.feldmann@uni-bonn.de).

[165]

**TÍTULO / TITLE:** - Atypical chemokine receptors predict lymph node metastasis and prognosis in patients with cervical squamous cell cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Apr 17. pii: S0090-8258(13)00235-7. doi: 10.1016/j.ygyno.2013.04.015.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.04.015](#)

**AUTORES / AUTHORS:** - Hou T; Liang D; Xu L; Huang X; Huang Y; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, GD 510060, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: Atypical chemokine receptors (ACRs), including CCX-CKR, DARC, and D6, have been reported to be involved in cancer invasion and metastasis. The objective of this study was to investigate the prognostic importance of ACRs in patients with cervical squamous cell carcinoma (CSCC). METHODS: The expression of three ACRs was investigated by immunohistochemical (IHC) examination in a total of 317 cervical specimens including 40 normal cervical tissues, 50 cases of carcinoma in situ of cervix (CIS), and 227 cases of CSCC by immunohistochemistry. RESULTS: The expression rate of DARC and CCX-CKR in CSCC, CIS, and normal cervix increased gradually ( $p < 0.01$ ). D6 expression is decreased in CSCC compared to either in CIS or in normal cervix ( $p < 0.05$ ). In addition, the expression of CCL2 and CCL19 was inversely associated with ACR expression ( $p < 0.05$ ), while that of LCA was positively correlated with ACR expression ( $p < 0.05$ ). Moreover, DARC expression, CCX-CKR expression, and ACR coexpression were negatively correlated with lymph node metastasis ( $P < 0.01$ ). D6 expression and ACR coexpression were negatively related to tumor size ( $p = 0.018$ ) and recurrence ( $p = 0.028$ ). In multivariate Cox regression analysis, CCX-CKR expression was a positive indicator for overall survival ( $p = 0.008$ ), and D6 expression was an independent predictor of both overall and recurrence-free survival ( $p = 0.041$ ) in CSCC. CONCLUSIONS: Our results suggest that the loss of ACRs may play important roles in the tumorigenesis and migration of cervical cancer. ACR expression may be considered as prognostic markers in patients with CSCC.

[166]

**TÍTULO / TITLE:** - Oncogenic mutations and microsatellite instability phenotype predict specific anatomical subsite in colorectal cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Hum Genet. 2013 Apr 10. doi: 10.1038/ejhg.2013.66.

●●Enlace al texto completo (gratis o de pago) [1038/ejhg.2013.66](#)

**AUTORES / AUTHORS:** - Corso G; Pascale V; Flauti G; Ferrara F; Marrelli D; Roviello F

**INSTITUCIÓN / INSTITUTION:** - Department of Human Pathology and Oncology, Section of General Surgery and Surgical Oncology, University of Siena, Siena, Italy.

**RESUMEN / SUMMARY:** - In colorectal cancer (CRC) oncogenic mutations such as KRAS alterations, are considered standard molecular biomarkers that predict the clinical benefit for targeted intervention with epidermal growth factor receptor (EGFR) inhibitors. In addition, these mutations are associated with specific anatomical area in colon tumor development, as BRAF mutations with the microsatellite instability (MSI). In this translational study, we aimed to assess the mutation frequencies of the EGFR (hotspot area and polyadenine deletions A13\_del), KRAS, BRAFV600E, and PIK3CA oncogenes in a series of 280 CRC patients. MSI phenotypes are also considered in this series. All patients' clinicopathological data were assessed for statistical analysis and its associations were validated. We verified multiple associations between oncogenic mutations and determined clinicopathological tumor features (1) EGFR A13\_deletions are associated with right colon carcinoma ( $P < 0.005$ ), mucinous histotype ( $P = 0.042$ ), G3 grading ( $P = 0.024$ ), and MSI status ( $P < 0.005$ ); (2) PIK3CA mutations are related mucinous histotype ( $P = 0.021$ ); (3) KRASG12 and KRASG13 mutations are correlated, respectively, with the left and right colon cancer development ( $P < 0.005$ ), and finally (4) MSI is associated with right colon tumors ( $P < 0.005$ ). Mostly, we verified a higher frequency rate of the KRASG13 and EGFR A13\_del oncogene mutations in right colon cancer; whereas KRASG12 codon mutation occurs more frequently in left colon cancers. In particular, we assessed that right vs left colon cancer are associated with specific molecular characteristics. These evidences, in association with clinicopathological data, can delineate novel approaches for the CRC classification and targeted intervention. *European Journal of Human Genetics* advance online publication, 10 April 2013; doi:10.1038/ejhg.2013.66.

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[167]

**TÍTULO / TITLE:** - YM155 induces caspase-8 dependent apoptosis through downregulation of survivin and Mcl-1 in human leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Biochem Biophys Res Commun.* 2013 May 24;435(1):52-7. doi: 10.1016/j.bbrc.2013.04.036. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.04.036](http://1016/j.bbrc.2013.04.036)

**AUTORES / AUTHORS:** - Feng W; Yoshida A; Ueda T

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Oncology, Faculty of Medicine, University of Fukui, 23 Shimoaizuki, Matsuoka, Eiheiji-Chou, Fukui 910-1193, Japan.

**RESUMEN / SUMMARY:** - Survivin, a member of the inhibitor of apoptosis protein (IAP) family, is highly expressed in various kinds of tumors. In the present study, we investigated the cytotoxic mechanism of YM155, a unique small-

molecule inhibitor of survivin, in human myelogenous leukemia cells. YM155 potently inhibited the cell growth of HL-60 and U937 cells with the half-maximal inhibitory concentration (IC50) value of 0.3nM and 0.8nM, respectively. YM155 significantly suppressed the levels of mRNA expression and protein of survivin in HL-60 and U937 cells. In addition, we also found that YM155 down-regulated the level of Mcl-1, another critical anti-apoptotic protein, in both HL-60 and U937 cells. Treatment of HL-60 and U937 cells with YM155 induced apoptosis concomitant with the activation of caspase-8 and caspase-3. Interestingly, we have found that caspase-8 inhibitor Z-IETD-FMK strongly inhibited YM155-induced apoptosis in HL-60 and U937 cells. When cells were pretreated with Z-IETD-FMK, the activation of caspase-3 was completely abolished, suggesting that caspase-8 may be involved in the activation of caspase-3 during YM155-induced apoptosis. We demonstrated for the first time that YM155 induces caspase-8 dependent apoptosis through downregulation of survivin and Mcl-1 in human leukemia cells.

[168]

**TÍTULO / TITLE:** - Combined modality doxorubicin-based chemotherapy and chitosan-mediated p53 gene therapy using double-walled microspheres for treatment of human hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomaterials. 2013 Jul;34(21):5149-62. doi: 10.1016/j.biomaterials.2013.03.044. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biomaterials.2013.03.044](#)

**AUTORES / AUTHORS:** - Xu Q; Leong J; Chua QY; Chi YT; Chow PK; Pack DW; Wang CH

**INSTITUCIÓN / INSTITUTION:** - Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576, Singapore; Department of Chemical and Biomolecular Engineering, University of Illinois, 600 S. Mathews Avenue, Urbana, IL 61801, USA.

**RESUMEN / SUMMARY:** - The therapeutic efficiency of combined chemotherapy and gene therapy on human hepatocellular carcinoma HepG2 cells was investigated using double-walled microspheres that consisted of a poly(D,L-lactic-co-glycolic acid) (PLGA) core surrounded by a poly(L-lactic acid) (PLLA) shell layer and fabricated via the precision particle fabrication (PPF) technique. Here, double-walled microspheres were used to deliver doxorubicin (Dox) and/or chitosan-DNA nanoparticles containing the gene encoding the p53 tumor suppressor protein (chi-p53), loaded in the core and shell phases, respectively. Preliminary studies on chi-DNA nanoparticles were performed to optimize gene transfer to HepG2 cells. The transfection efficiency of chi-DNA nanoparticles was optimal at an N/P ratio of 7. In comparison to the 25-kDa branched

polyethylenimine (PEI), chitosan showed no inherent toxicity towards the cells. Next, the therapeutic efficiencies of Dox and/or chi-p53 in microsphere formulations were compared to free drug(s) and evaluated in terms of growth inhibition, and cellular expression of tumor suppressor p53 and apoptotic caspase 3 proteins. Overall, the combined Dox and chi-p53 treatment exhibited enhanced cytotoxicity as compared to either Dox or chi-p53 treatments alone. Moreover, the antiproliferative effect was more substantial when cells were treated with microspheres than those treated with free drugs. High p53 expression was maintained during a five-day period, and was largely due to the controlled and sustained release of the microspheres. Moreover, increased activation of caspase 3 was observed, and was likely to have been facilitated by high levels of p53 expression. Overall, double-walled microspheres present a promising dual anticancer delivery system for combined chemotherapy and gene therapy.

[169]

**TÍTULO / TITLE:** - Prognostic value of residual fluorescent tissue in glioblastoma patients after gross total resection in 5-aminolevulinic Acid-guided surgery.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neurosurgery. 2013 Jun;72(6):915-21. doi: 10.1227/NEU.0b013e31828c3974.

●●Enlace al texto completo (gratis o de pago)

[1227/NEU.0b013e31828c3974](#)

**AUTORES / AUTHORS:** - Aldave G; Tejada S; Pay E; Marigil M; Bejarano B; Idoate MA; Diez-Valle R

**INSTITUCIÓN / INSTITUTION:** - \*Department of Neurosurgery, Clinica Universidad de Navarra, Pamplona, España; double daggerDepartment of Pathology, Clinica Universidad de Navarra, Pamplona, España.

**RESUMEN / SUMMARY:** - BACKGROUND: : There is evidence in the literature supporting that fluorescent tissue signal in fluorescence-guided surgery extends farther than tissue highlighted in gadolinium in T1 sequence magnetic resonance imaging (MRI), which is the standard to quantify the extent of resection. OBJECTIVE: : To study whether the presence of residual fluorescent tissue after surgery carries a different prognosis for glioblastoma (GBM) cases with complete resection confirmed by MRI. METHODS: : A retrospective review in our center found 118 consecutive patients with high-grade gliomas operated on with the use of fluorescence-guided surgery with 5-aminolevulinic acid. Within that series, the 52 patients with newly diagnosed GBM and complete resection of enhancing tumor (CRET) in early MRI were selected for analysis. We studied the influence of residual fluorescence in the surgical field on overall survival and neurological complication rate. Multivariate analysis included potential relevant factors: age, Karnofsky Performance Scale, O-methylguanine methyltransferase methylation promoter status, tumor eloquent location,

preoperative tumor volume, and adjuvant therapy. RESULTS: : The median overall survival was 27.0 months (confidence interval = 22.4-31.6) in patients with nonresidual fluorescence (n = 25) and 17.5 months (confidence interval = 12.5-22.5) for the group with residual fluorescence (n = 27) (P = .015). The influence of residual fluorescence was maintained in the multivariate analysis with all covariables, hazard ratio = 2.5 (P = .041). The neurological complication rate was 18.5% in patients with nonresidual fluorescence and 8% for the group with residual fluorescence (P = .267). CONCLUSION: : GBM patients with CRET in early MRI and no fluorescent residual tissue had longer overall survival than patients with CRET and residual fluorescent tissue. ABBREVIATIONS: : 5-ALA, 5-aminolevulinic acidCRET, complete resection of enhancing tumorDC, dendritic cellEOR, extent of resectionFGS, fluorescence-guided surgeryGBM, glioblastomaGTR, gross total resectionKPS, Karnofsky Performance ScaleMGMT, O-methylguanine methyltransferaseOS, overall survivalT1Gd, gadolinium in T1 sequence.

[170]

**TÍTULO / TITLE:** - GDNF-RET signaling in ER-positive breast cancers is a key determinant of response and resistance to aromatase inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 May 6.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-4265](https://doi.org/10.1158/0008-5472.CAN-12-4265)

**AUTORES / AUTHORS:** - Morandi A; Martin LA; Gao Q; Pancholi S; Mackay A; Robertson D; Zvelebil M; Dowsett M; Plaza-Menacho I; Isacke CM

**INSTITUCIÓN / INSTITUTION:** - Breakthrough Breast Cancer Research Centre, Institute of Cancer Research.

**RESUMEN / SUMMARY:** - Most breast cancers at diagnosis are estrogen receptor (ER)-positive and depend on estrogen for growth and survival. Blocking estrogen biosynthesis by aromatase inhibitors (AI) has therefore become a first-line endocrine therapy for post-menopausal women with ER-positive breast cancers. Despite providing substantial improvements in patient outcome, AI resistance remains a major clinical challenge. The receptor tyrosine kinase RET and its co-receptor GFR $\alpha$ 1 are upregulated in a subset of ER-positive breast cancers, and the RET ligand, glial-derived neurotrophic factor (GDNF) is upregulated by inflammatory cytokines. Here we report the findings of a multidisciplinary strategy to address the impact of GDNF-RET signaling in the response to AI treatment. In breast cancer cells in 2D and 3D culture, GDNF-mediated RET signaling is enhanced in a model of AI resistance. Further, GDNF-RET signaling promoted the survival of AI-resistant cells and elicited resistance in AI-sensitive cells. Both these effects were selectively reverted by the RET kinase inhibitor NVP-BBT594. Gene expression profiling in ER-positive cancers defined a proliferation-independent GDNF-response signature that

prognosed poor patient outcome and, more importantly, predicted poor response to AI treatment with the development of resistance. We validated these findings by demonstrating increased RET protein expression levels in an independent cohort of AI-resistant patient specimens. Together, our results establish GDNF-RET signaling as a rational therapeutic target to combat or delay the onset of AI resistance in breast cancer.

[171]

**TÍTULO / TITLE:** - High expression of Transient potential receptor C6 correlated with poor prognosis in patients with esophageal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):607. doi: 10.1007/s12032-013-0607-7. Epub 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0607-7](#)

**AUTORES / AUTHORS:** - Zhang SS; Wen J; Yang F; Cai XL; Yang H; Luo KJ; Liu QW; Hu RG; Xie X; Huang QY; Chen JY; Fu JH; Hu Y

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, Guangzhou, People's Republic of China.

**RESUMEN / SUMMARY:** - TRPC6 plays a crucial role in the tumor progression of various cancers. The relation between the expression of TRPC6 and clinical prognosis has not been studied yet. Our study was to elucidate the role of TRPC6 in predicting outcomes of patients with esophageal squamous cell carcinoma (ESCC). Fresh frozen samples were collected immediately from 172 patients with ESCC after surgical resection from 2003 to 2008 at Sun Yat-sen University Cancer Center, including 45 pairs of tumor tissues and nontumor tissues. TRPC6 expression was measured by quantitative real-time PCR and Western blotting analyses. TRPC6 mRNA and protein were up-regulated in ESCC tissues when compared with the paired nontumor tissues. High expression of TRPC6 mRNA was associated with the higher pT status ( $P = 0.016$ ) and pathological staging ( $P = 0.040$ ). The 5-year disease-specific survival in the high expression of TRPC6 mRNA group ( $>188.98$ ,  $n = 81$ ) is poorer than that in low-level expression group ( $\leq 188.98$ ,  $n = 91$ ) (42.1 vs. 62.7 %,  $P = 0.004$ ). Stratified analysis according to the pathological stage revealed its discernibility on DSS was only pronounced in patients with pStage III ( $P = 0.015$ ). Cox multivariate analysis revealed that pN category ( $P < 0.001$ ; Relative risk, 2.897, 95 % CI 1.830-4.585) and the expression of TRPC6 mRNA ( $P = 0.006$ ; Relative risk, 1.863, 95 % CI 1.196-2.902) were independent prognostic factors. TRPC6 mRNA overexpression correlated with poor prognosis in patients with ESCC and might serve as a novel prognostic biomarker for resected ESCC patients in advanced stage.

[172]

**TÍTULO / TITLE:** - Anti-CD33-antibodies labelled with the alpha-emitter Bismuth-213 kill CD33-positive acute myeloid leukaemia cells specifically by activation of caspases and break radio- and chemoresistance by inhibition of the anti-apoptotic proteins X-linked inhibitor of apoptosis protein and B-cell lymphoma-extra large.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 May 16. pii: S0959-8049(13)00310-9. doi: 10.1016/j.ejca.2013.04.008.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.04.008](#)

**AUTORES / AUTHORS:** - Friesen C; Roscher M; Hormann I; Leib O; Marx S; Moreno J; Miltner E

**INSTITUCIÓN / INSTITUTION:** - Center for Biomedical Research, University Ulm, Helmholtzstrasse 8/1, 89081 Ulm, Germany; Institute for Legal Medicine, University Ulm, Prittwitzstrasse 6, 89075 Ulm, Germany. Electronic address: [claudia.friesen@uni-ulm.de](mailto:claudia.friesen@uni-ulm.de).

**RESUMEN / SUMMARY:** - AIM: The emerging interest in radioimmunotherapies employing alpha-emitters for cancer treatment like high risk-leukaemia leads to the question of how these radionuclides exhibit their cytotoxicity. To clarify the molecular mechanisms of cell death induction, we investigated the molecular effects of the alpha-emitter Bismuth-213 (Bi-213) bound to a monoclonal anti-CD33-antibody ([Bi-213]anti-CD33) on the cell cycle and on apoptosis induction in sensitive as well as in beta- and gamma-radiation-resistant CD33-positive acute myeloid leukaemia (AML) cells. METHODS: The cytotoxic potential of the radioimmunoconjugate [Bi-213]anti-CD33 was analysed in the CD33-expressing human AML cell line HL-60 and in radiation- and chemoresistant HL-60-derived cell lines. Cell cycle and apoptosis induction analyses were performed via flow cytometry. Activation of apoptosis pathways was determined by immunodetection. RESULTS: [Bi-213]anti-CD33 induced apoptotic cell death in CD33-positive AML cells specifically. Molecular analyses revealed that the intrinsic mitochondrial pathway of apoptosis was activated resulting in caspase-9 activation. In the apoptotic executioner cascade caspase-3 was activated and its substrate poly (ADP-ribose) polymerase (PARP) was cleaved. Notably, [Bi-213]anti-CD33 overcame radio- and chemoresistance by reversing deficient activation of apoptosis pathways in resistant CD33-positive AML cells and by the downregulation of inhibitors of apoptosis B-cell lymphoma-extra large (Bcl-xL) and X-linked inhibitor of apoptosis protein (XIAP) involved in leukaemia resistance. CONCLUSION: [Bi-213]anti-CD33 exhibits its cytotoxic effects specifically in CD33-expressing AML cells via induction of the intrinsic, mitochondrial pathway of apoptosis. The abrogation of chemo- and radioresistances and the reactivation of apoptotic pathways seem to be promising for the treatment of patients with so far untreatable resistant AML and

underline the importance of this emerging therapeutic approach of targeted alpha-therapies.

[173]

**TÍTULO / TITLE:** - A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):441-51. doi: 10.1007/s10549-013-2573-3. Epub 2013 May 30.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2573-](#)

[3](#)

**AUTORES / AUTHORS:** - Iwata H; Masuda N; Ohno S; Rai Y; Sato Y; Ohsumi S; Hashigaki S; Nishizawa Y; Hiraoka M; Morimoto T; Sasano H; Saeki T; Noguchi S

**INSTITUCIÓN / INSTITUTION:** - Aichi Cancer Center Hospital, Aichi, Japan.

**RESUMEN / SUMMARY:** - The aromatase inhibitors exemestane and anastrozole are approved in Japan for first-line treatment of postmenopausal patients with advanced, hormone-receptor-positive breast cancer. This phase 3, randomized, double-blind study directly compared time to progression (TTP) for exemestane and anastrozole therapy in this patient population. Eligible patients were randomized to receive exemestane 25 mg or anastrozole 1 mg, each once daily. The primary endpoint was TTP based on assessment by an expert radiologic images review committee (ERIRC). Secondary endpoints included investigator-assessed TTP, time to treatment failure, overall survival, objective response rate, clinical benefit rate, and safety. A total 298 patients were randomized to receive exemestane (n = 149; mean age 63.4 years) or anastrozole (n = 149; mean age 64.0 years). Median ERIRC-assessed TTP was 13.8 and 11.1 months (hazard ratio = 1.007; 95 % confidence interval [CI]: 0.771, 1.317) and median investigator-assessed TTP was 13.8 and 13.7 months (hazard ratio = 1.059; 95 % CI: 0.816, 1.374) in the exemestane and anastrozole arms, respectively. Median overall survival was 60.1 months in the anastrozole arm and was not reached in the exemestane arm at data cutoff. The objective response rate was 43.9 % (95 % CI: 35.3, 52.8) and 39.1 % (95 % CI: 30.6, 48.1) in the exemestane and anastrozole arms, respectively. Treatment-related adverse events grade  $\geq$ 3 occurred in 9.4 and 6.0 % of patients, and treatment-related serious adverse events occurred in 4.0 and 3.4 % of patients in the exemestane and anastrozole arms, respectively. In this study, the efficacy and safety profiles of exemestane were similar to those of anastrozole in Japanese patients with advanced, hormone-receptor-positive breast cancer; however, TTP non-inferiority of exemestane versus anastrozole was not confirmed.

[174]

**TÍTULO / TITLE:** - Prognostic Significance in Breast Cancer of a Gene Signature Capturing Stromal PDGF Signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Pathol. 2013 Jun;182(6):2037-47. doi: 10.1016/j.ajpath.2013.02.018. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ajpath.2013.02.018](#)

**AUTORES / AUTHORS:** - Frings O; Augsten M; Tobin NP; Carlson J; Paulsson J; Pena C; Olsson E; Veerla S; Bergh J; Ostman A; Sonnhämmer EL

**INSTITUCIÓN / INSTITUTION:** - Stockholm Bioinformatics Centre, Science for Life Laboratory, Solna, Sweden; Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden.

**RESUMEN / SUMMARY:** - In this study, we describe a novel gene expression signature of platelet-derived growth factor (PDGF)-activated fibroblasts, which is able to identify breast cancers with a PDGF-stimulated fibroblast stroma and displays an independent and strong prognostic significance. Global gene expression was compared between PDGF-stimulated human fibroblasts and cultured resting fibroblasts. The most differentially expressed genes were reduced to a gene expression signature of 113 genes. The biological significance and prognostic capacity of this signature were investigated using four independent clinical breast cancer data sets. Concomitant high expression of PDGFbeta receptor and its cognate ligands is associated with a high PDGF signature score. This supports the notion that the signature detects tumors with PDGF-activated stroma. Subsequent analyses indicated significant associations between high PDGF signature score and clinical characteristics, including human epidermal growth factor receptor 2 positivity, estrogen receptor negativity, high tumor grade, and large tumor size. A high PDGF signature score is associated with shorter survival in univariate analysis. Furthermore, the high PDGF signature score acts as a significant marker of poor prognosis in multivariate survival analyses, including classic prognostic markers, Ki-67 status, a proliferation gene signature, or other recently described stroma-derived gene expression signatures.

[175]

**TÍTULO / TITLE:** - Antitumor T cell responses in bladder cancer are directed against a limited set of antigens and are modulated by regulatory T cells and routine treatment approaches.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Apr 27. doi: 10.1002/ijc.28233.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28233](#)

**AUTORES / AUTHORS:** - Horn T; Grab J; Schusdzarra J; Schmid S; Maurer T; Nawroth R; Wolf P; Pritsch M; Gschwend JE; Kubler HR; Beckhove P

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Klinikum rechts der Isar, Technische Universität München, Germany; Translational Immunology Unit, German Cancer Research Center, Heidelberg, Germany.

**RESUMEN / SUMMARY:** - Regulatory T cells (Treg) play a key role in cancer immune escape. We identified target antigens of spontaneous tumor-specific T cell responses in urothelial carcinoma (UC) and evaluated their modulation by treatment and Treg. We determined Treg target antigens in UC. Fifty-six UC and thirteen control patients were prospectively enrolled. Blood was drawn before and after routine treatment. Changes in Treg frequency were measured by fluorescence cytometry and the T effector cell (Teff) response against a set of nine tumor-associated antigens (TAA) was monitored with an IFN-gamma ELISpot. Antigen specificity of Treg was determined by their increased capacity to inhibit after TAA-specific activation the proliferation of an autologous T cell population. The highest difference in the overall response rate for the total T cell population was observed for EGFR (UC: 23%, controls 0%). After depleting Treg also NYESO1 (19%, 0%) and MUC20 (27%, 0%) were more frequently recognized in UC patients. In metastasized patients the TAA-directed T cell response was augmented by Treg depletion. Tumor resection seemed to diminish Treg suppression of TAA-specific immunity, while chemotherapy had no effect. We demonstrated the existence of TAA-specific Treg in UC, which share antigen specificities with Teff. The coexistence of TAA-specific Treg and Teff was very rare. Treg frequencies in the peripheral blood were not changed by therapy. In summary, we identified potentially immunologically relevant TAA in UC. TAA-specific T cell responses against these antigens are suppressed by Treg. We identified TAA-specific Treg in UC patients, which do not cooccur with TAA-specific Teff. © 2013 Wiley Periodicals, Inc.

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[176]

**TÍTULO / TITLE:** - 5'-Triphosphate-siRNA Against Survivin Gene Induces Interferon Production and Inhibits Proliferation of Lung Cancer Cells In Vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Immunother. 2013 Jun;36(5):294-304. doi: 10.1097/CJI.0b013e318294183b.

●●Enlace al texto completo (gratis o de pago)

[1097/CJI.0b013e318294183b](#)

**AUTORES / AUTHORS:** - Wang K; Chen X; Yan F; Xing Y; Yang X; Tu J; Chen Z

**INSTITUCIÓN / INSTITUTION:** - \*Department of Biochemistry and Molecular Biology, Anhui Medical University, Hefei, Anhui Province daggerDivision of Infection and Immunity, Department of Electromagnetic and Laser Biology, Beijing Institute of Radiation Medicine, Beijing, China double daggerAustralian School of Advanced Medicine, Macquarie University, Sydney, NSW, Australia.

**RESUMEN / SUMMARY:** - Survivin is a new member of the inhibitors of apoptosis family and upregulated in various human malignancies including human lung cancer. In this study, we proposed a new strategy for RNA interference (RNAi)-mediated anticancer therapy combining activation of interferon production with RNAi using 5'-triphosphate-siRNA (3p-siRNA) against survivin gene. We designed and generated 3p-siRNA targeting human survivin gene (3p-survivin-siRNA). The findings reported here demonstrated that 3p-survivin-siRNA induced a 3p-dependent type-I interferon response when transfected into human lung cancer cells. The 3p-survivin-siRNA significantly inhibited lung cancer cell proliferation in a 3p-dependent manner. The anticancer effect of 3p-survivin-siRNA was superior to that of conventional siRNA. The expression level of survivin in 3p-survivin-siRNA-treated A549 cells was significantly lower than that of siRNA. Furthermore, when 3p-survivin-siRNA silencing approach was combined with radiation treatment, 3p-survivin-siRNA increases the cytotoxicity of A549 cells and induces more cells to undergo apoptosis. In conclusion, our results suggest that 3p-survivin-siRNA could act as a powerful bifunctional molecule with potential for developing promising radiosensitization therapeutics against human lung cancer.

[177]

**TÍTULO / TITLE:** - Subclinical pretreatment sensory deficits appear to predict the development of pain and numbness in patients with multiple myeloma undergoing chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Jun;71(6):1531-40. doi: 10.1007/s00280-013-2152-7. Epub 2013 Mar 31.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2152-](#)

[7](#)

**AUTORES / AUTHORS:** - Vichaya EG; Wang XS; Boyette-Davis JA; Mendoza TR; He Z; Thomas SK; Shah N; Williams LA; Cleeland CS; Dougherty PM

**INSTITUCIÓN / INSTITUTION:** - Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

**RESUMEN / SUMMARY:** - PURPOSE: Chemotherapy-induced peripheral neuropathy is a major complication in the treatment for cancer, including multiple myeloma (MM). Patients may develop painful and non-painful (e.g., numbness) neuropathy symptoms that impair function and often persist after therapy is terminated. This study tested the hypothesis that baseline subclinical neuropathy, as assessed by sensory thresholds, is related to the development of neuropathy symptoms (e.g., pain and numbness) in patients with MM undergoing treatment with chemotherapy. METHODS: Patients (n = 56) who had undergone two or fewer cycles of induction therapy and who had no evident neuropathy were assessed using quantitative sensory tests to determine multiple-modality sensory thresholds. Patient-reported pain and numbness were

assessed through induction therapy (16 weeks) via the MD Anderson Symptom Inventory. A subset of participants (n = 15) continued reporting on their symptoms for an additional 16 weeks ("maintenance phase"). RESULTS: Patients with sharpness detection deficits at baseline (n = 11, 20 % of sample) reported less severe pain and numbness during induction therapy and less numbness during maintenance therapy (P < 0.05). During the maintenance phase, patients with warmth detection deficits (n = 5, 38 % of sample) reported more severe pain and numbness, and those with skin temperature deficits (n = 7, 47 % of maintenance sample) reported more severe pain (P < 0.05). These deficits were related to patient reported difficulty walking, a common symptom of peripheral neuropathy. CONCLUSION: Our results suggest that baseline subclinical sensory deficits may be related to a patient's risk for developing chemotherapy-induced peripheral neuropathy.

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[178]

**TÍTULO / TITLE:** - Ibrutinib: A Novel Bruton's Tyrosine Kinase Inhibitor With Outstanding Responses in Patients With Chronic Lymphocytic Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.796049](https://doi.org/10.1182/10428194.2013.796049)

**AUTORES / AUTHORS:** - Barrientos J; Rai K

**RESUMEN / SUMMARY:** - Abstract New treatment options are urgently needed for patients with relapsed chronic lymphocytic leukemia (CLL) who fail to respond to currently available therapies or cannot achieve a sustained response. Moreover, targeted agents with less myelotoxicity are necessary to treat patients with multiple comorbidities who would otherwise be unable to tolerate standard regimens. Ibrutinib, a Bruton's Tyrosine Kinase inhibitor, has shown highly encouraging results in phase I/II trials in patients with treatment-naive, relapsed, and refractory CLL even in the presence of high risk disease or poor prognostic markers. In phase I/II trials, ibrutinib 420mg or 840mg -given continuously as single agent or at a dose of 420mg daily in combination with a monoclonal antibody or chemoimmunotherapy- has been associated with high response rates and durable clinical remissions. Phase II and III trials are currently underway for treatment-naive patients, relapsed/refractory patients, and for those patients harboring a 17p deletion.

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[179]

**TÍTULO / TITLE:** - Combined administration of FVIII and rFVIIa improves haemostasis in haemophilia A patients with high-responding inhibitors - a thrombin generation-guided pilot study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haemophilia. 2013 May 10. doi: 10.1111/hae.12181.

●●Enlace al texto completo (gratis o de pago) [1111/hae.12181](http://1111/hae.12181)

**AUTORES / AUTHORS:** - Livnat T; Martinowitz U; Azar-Avivi S; Zivelin A; Brutman-Barazani T; Lubetsky A; Kenet G

**INSTITUCIÓN / INSTITUTION:** - The Israeli National Hemophilia Center and Thrombosis Unit, Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Tel Aviv University, Tel Hashomer, Israel.

**RESUMEN / SUMMARY:** - Treatment of haemophilia A patients with inhibitors is challenging, and may require individually tailored regimens. Whereas low titre inhibitor patients may respond to high doses of factor VIII (FVIII), high-responding inhibitor patients render replacement therapy ineffective and often require application of bypassing agents. Thrombin generation (TG) assays may be used to monitor haemostasis and/or predict patients' response to bypass agents. In this study we defined by TG, the potential contribution of FVIII to recombinant activated factor VII (rFVIIa)-induced haemostasis in inhibitor plasma. Based upon results, prospectively designed individual regimens of coadministration of rFVIIa and FVIII were applied. Plasma samples from 14 haemophilia patients with inhibitors (including high titre inhibitors) were tested. The response to increasing concentrations of FVIII, rFVIIa or both was assayed by TG. Eight patients, chosen following consent and at physician's discretion, comprised the combined FVIII-rFVIIa therapy clinical study cohort. Combined spiking with FVIII/rFVIIa improved TG induced by rFVIIa alone in all inhibitor plasmas. Combined rFVIIa and FVIII therapy was applied during bleeding or immune tolerance to eight patients, for a total of 393 episodes. Following a single combined dose, 90% haemostasis was documented and neither thrombosis nor any complications evolved. During study period decline of inhibitor levels and bleeding frequency were noted. Pre-analytical studies enabled us to prospectively tailor individual therapy regimens. We confirmed for the first time that the in vitro advantage of combining FVIII and rFVIIa, indeed accounts for improved haemostasis and may safely be applied to inhibitor patients.

[180]

**TÍTULO / TITLE:** - Insulin-like growth factor 2 mRNA binding protein 3 expression is an independent prognostic factor in pediatric pilocytic and pilomyxoid astrocytoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neuropathol Exp Neurol. 2013 May;72(5):442-9. doi: 10.1097/NEN.0b013e31829023dd.

●●Enlace al texto completo (gratis o de pago)

[1097/NEN.0b013e31829023dd](http://1097/NEN.0b013e31829023dd)

**AUTORES / AUTHORS:** - Barton VN; Donson AM; Birks DK; Kleinschmidt-DeMasters BK; Handler MH; Foreman NK; Rush SZ

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, University of Colorado, Aurora, CO, USA.

**RESUMEN / SUMMARY:** - Prognostic factors in pilocytic astrocytomas (PAs) and pilomyxoid astrocytomas (PMAs) include extent of resection, location, and age, but no molecular markers have been established. Insulin-like growth factor 2 mRNA binding protein 3 (IMP3, IGF2BP3) is predictive of an unfavorable prognosis in other tumors, including high-grade astrocytomas, but its role in PA/PMA is unknown. This study aimed to determine the expression and prognostic value of IMP3 in pediatric PA/PMAs. Insulin-like growth factor 2 mRNA binding protein 3 protein expression was examined by immunohistochemistry in 77 pediatric PAs (n = 70) and PMAs (n = 7) and scored on a subjective scale. Strong diffuse staining for IMP3 was observed in 31% (24 of 77) of tumors and associated with a shorter progression-free survival (hazard ratio, 2.63; p = 0.008). This cohort confirmed previously identified prognostic factors, including extent of resection, age, and tumor location. Currently, only clinical factors are weighed to stratify risk for patients and to identify those who should receive further therapy. Multivariate analyses identified IMP3 expression as an independent prognostic factor when combined with high-/low-risk stratification (hazard ratio, 2.45; p = 0.016). High IMP3, as assessed by immunohistochemistry, has potential use as an additional predictor of poor prognosis in pediatric PA/PMAs and warrants evaluation in larger cohorts.

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[181]

**TÍTULO / TITLE:** - Telomerase downregulation induces proapoptotic genes expression and initializes breast cancer cells apoptosis followed by DNA fragmentation in a cell type dependent manner.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1007/s11033-013-2600-](#)

[9](#)

**AUTORES / AUTHORS:** - Rubis B; Holysz H; Gladych M; Toton E; Paszel A; Lisiak N; Kaczmarek M; Hofmann J; Rybczynska M

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Chemistry and Molecular Diagnostics, Poznan University of Medical Sciences, ul. Przybyszewskiego 49, 60-355, Poznan, Poland, [blazejr@ump.edu.pl](mailto:blazejr@ump.edu.pl).

**RESUMEN / SUMMARY:** - The aim of the study was to analyze the consequence of silencing genes coding for the key subunits of the telomerase complex, i.e. TERT, TERC and TP1 in human breast cancer MCF7 and MDA-MB-231 cells. The transfection was performed using Lipofectamine2000 and pooled siRNAs. The cytotoxic and/or antiproliferative effect of siRNA was measured by the SRB assay, the cell cycle was analysed by flow cytometry and DNA fragmentation by TUNEL analysis. Telomerase activity was assessed by TRAP, followed by

PAGE and ELISA assays. Telomerase downregulation was also assessed using qPCR in order to estimate the changes in the expression profile of genes engaged in apoptosis. It was revealed that treatment of breast cancer cells with different siRNAs (100 nM) resulted in a cell type and time-dependent effects. The downregulation of telomerase subunits was followed by reduction of telomerase activity down to almost 60 % compared to control cells. However, a significant effect was only observed when the TERT subunit was downregulated. Its silencing resulted in a significant ( $p < 0.05$ ) increase of apoptosis (over 10 % in MCF7 and about 5 % in MDA-MB-231 cells, corresponding to the Annexin V assay) and DNA fragmentation (almost 30 % in MCF7 and over 25 % in MDA-MB-231 cells). Interestingly, also several proapoptotic genes were induced after the downregulation of the key telomerase subunit, including Bax, Bik or caspase-1 and caspase-14, as well as NGFR and TNFSF10 which were upregulated twice and more.

[182]

**TÍTULO / TITLE:** - Apoptotic and Proliferative Characteristics of Proliferation Centers in Lymph Node Sections of Chronic Lymphocytic Leukemia Patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 23.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.806802](https://doi.org/10.1186/10428194.2013.806802)

**AUTORES / AUTHORS:** - Sachanas S; Levidou G; Angelopoulou MK; Moschogiannis M; Yiakoumis X; Kalpadakis C; Vassilakopoulos TP; Kontopidou F; Tsirkinidis P; Dimitrakopoulou A; Kokoris S; Dimitriadou E; Kyrtsonis MC; Panayiotidis P; Papadaki H; Patsouris E; Korkolopoulou P; Pangalis GA

**RESUMEN / SUMMARY:** - ABSTRACT We have analyzed the immunohistochemical expression of a wide range of molecules, along with the proliferation rate separately in the proliferation centers (PCs) and in the rest of tumor area on lymph node or spleen sections of CLL patients. Fas, FasL and c-FLIP were observed both within and outside the PCs in all cases. However only the difference in FasL expression between the PCs and the non-PC areas attained statistical significance. Median survivin expression in the PCs was higher compared to the non-PC areas. Cleaved-caspase 3 was expressed in very low levels both within and outside PCs while the BCL-2 protein was expressed in high levels in all cases in both tumor compartments. Multivariate analysis demonstrated that concurrent overexpression of Fas/FasL/c-FLIP in the PCs was correlated with worse outcome for progression free survival as well as for overall survival.

[183]

**TÍTULO / TITLE:** - An armed oncolytic measles vaccine virus eliminates human hepatoma cells independently of apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gene Ther. 2013 May 30. doi: 10.1038/gt.2013.28.

●●Enlace al texto completo (gratis o de pago) [1038/gt.2013.28](#)

**AUTORES / AUTHORS:** - Lampe J; Bossow S; Weiland T; Smirnow I; Lehmann R; Neubert W; Bitzer M; Lauer UM

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Division of Hepatology, Gastroenterology and Infectiology, Medical University Hospital, Tübingen, Germany.

**RESUMEN / SUMMARY:** - Due to late diagnosis and a pronounced chemoresistance, most patients with hepatocellular carcinoma (HCC) have an overall poor prognosis. Measles vaccine viruses (MeV) have been shown to possess anti-tumor properties and their efficacy has been enhanced by arming with suicide genes. To test armed MeV for the treatment of HCC, we equipped it with the suicide gene Super-cytosine deaminase (SCD) and tested the efficacy in cell culture and in a mouse xenograft model of human HCC. Prodrug conversion was investigated in cell culture and quantified by high-performance liquid chromatography. We observed a strong oncolytic activity of MeV-SCD against human HCC in vitro and in vivo. The prodrug was efficiently converted in infected cells leading to a significant enhancement of the cytotoxic effect. Treatment of HCC xenografts with MeV caused long-term virus replication in tumor tissue. We show that the suicide gene therapy induces an apoptosis-like cell death but is not dependent on intact apoptosis pathways. These results demonstrate that MeV-based suicide gene therapy is a promising novel therapy regimen for HCC overcoming resistance towards conventional therapy. The independence from apoptosis raises hopes for the treatment of patients whose tumor cells exert defects in this cell death mechanism. Gene Therapy advance online publication, 30 May 2013; doi:10.1038/gt.2013.28.

[184]

**TÍTULO / TITLE:** - Predictive factors for all-trans retinoic acid-related differentiation syndrome in patients with acute promyelocytic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 Jul;37(7):747-51. doi: 10.1016/j.leukres.2013.04.011. Epub 2013 May 1.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.04.011](#)

**AUTORES / AUTHORS:** - Leblebjian H; Deangelo DJ; Skirvin JA; Stone RM; Wadleigh M; Werner L; Neuberg DS; Bartel S; McDonnell AM

**INSTITUCIÓN / INSTITUTION:** - Dana Farber Cancer Institute, Department of Pharmacy Services, Boston, MA, USA. Electronic address:

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**RESUMEN / SUMMARY:** - All-trans retinoic acid (ATRA) used for the treatment of APL can lead to the development of differentiation syndrome (DS), a potentially life threatening complication. Since ATRA is metabolized by cytochrome P450 (CYP) enzymes, we sought to identify drug interactions that might be associated with a higher risk for the development of DS in addition to other predictive factors related to the incidence of DS. We identified 60 consecutive patients with APL treated at our institution with ATRA from May 2004 until January 2010. Of the 60 patients identified, 29 (48%) developed DS within a median of 5 days (range 1-31) of ATRA initiation. We did not find any difference in overall incidence of DS whether patients were on concurrent CYP 2C8, 2C9 or 3A4 inhibitors, inducers or substrates. In multivariable analysis, higher peripheral blood blast counts on admission ( $p=0.04$ ) as well as higher body mass index ( $p=0.003$ ) were associated with developing DS. Out of the 29 patients with DS, there were 4 early deaths of which 2 were attributed to DS compared to no early deaths in the patients who did not develop DS ( $p=0.05$ ). Regarding disease-related outcomes, only CR rate was different between patients developing DS versus those who did not develop DS.

[185]

**TÍTULO / TITLE:** - Quercetin and epigallocatechin gallate inhibit glucose uptake and metabolism by breast cancer cells by an estrogen receptor-independent mechanism.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Cell Res. 2013 May 9. pii: S0014-4827(13)00195-X. doi: 10.1016/j.yexcr.2013.05.001.

●●Enlace al texto completo (gratis o de pago)

[1016/j.yexcr.2013.05.001](#)

**AUTORES / AUTHORS:** - Moreira L; Araujo I; Costa T; Correia-Branco A; Faria A; Martel F; Keating E

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry (U38-FCT), Faculty of Medicine of University of Porto, Alameda Prof. Hernani Monteiro, 4200-319 Porto, Portugal. Electronic address: [lilianam87@gmail.com](mailto:lilianam87@gmail.com).

**RESUMEN / SUMMARY:** - In this study we characterized 3H-2-deoxy-d-glucose (3H-DG) uptake by the estrogen receptor (ER)-positive MCF7 and the ER-negative MDA-MB-231 human breast cancer cell lines and investigated the effect of quercetin (QUE) and epigallocatechin gallate (EGCG) upon 3H-DG uptake, glucose metabolism and cell viability and proliferation. In both MCF7 and MDA-MB-231 cells 3H-DG uptake was (a) time-dependent, (b) saturable with similar capacity ( $V_{max}$ ) and affinity ( $K_m$ ), (c) potently inhibited by cytochalasin B, an inhibitor of the facilitative glucose transporters (GLUT), (d) sodium-independent and (e) slightly insulin-stimulated. This suggests that 3H-DG uptake by both cell types is mediated by members of the GLUT family, including the insulin-responsive GLUT4 or GLUT12, while being independent of

the sodium-dependent glucose transporter (SGLT1). QUE and EGCG markedly and concentration-dependently inhibited 3H-DG uptake by MCF7 and by MDA-MB-231 cells, and both compounds blocked lactate production by MCF7 cells. Additionally, a 4h-treatment with QUE or EGCG decreased MCF7 cell viability and proliferation, an effect that was more potent when glucose was available in the extracellular medium. Our results implicate QUE and EGCG as metabolic antagonists in breast cancer cells, independently of estrogen signalling, and suggest that these flavonoids could serve as therapeutic agents/adjuvants even for ER-negative breast tumors.

[186]

**TÍTULO / TITLE:** - A Kinome-Wide siRNA Screen Identifies Multiple Roles for Protein Kinases in Hypoxic Stress Adaptation, Including Roles for IRAK4 and GAK in Protection against Apoptosis in VHL-/- Renal Carcinoma Cells, Despite Activation of the NF-kappaB Pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biomol Screen. 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago)

[1177/1087057113484803](#)

**AUTORES / AUTHORS:** - Pan J; Zhang J; Hill A; Lapan P; Berasi S; Bates B; Miller C; Haney S

**INSTITUCIÓN / INSTITUTION:** - 1Applied Genomics, Department of Biological Technologies, Wyeth Research, Cambridge, MA, USA.

**RESUMEN / SUMMARY:** - Hypoxia induces changes to cancer cells that make them more resistant to treatment. We have looked at signaling pathways that facilitate these changes by screening the human kinome for effects on hypoxic responses in SW480 colon cancer cells. Hits identified in the screen were examined for effects on multiple molecular responses to hypoxia, including the endoplasmic reticulum stress and DNA damage responses in colon, melanoma, and renal cancer lines. To validate the hits from the small interfering RNA studies, we developed cell lines expressing stable short hairpin RNAs (shRNAs) in the A498 renal carcinoma cell line. Several lines, including those expressing shRNAs against DYRK1B, GAK, IHPK2, IRAK4, and MATK, showed an inability to form spheroid cultures. In addition, shRNAs targeting IRAK4 and GAK were incapable of 2D growth under anoxia. In the GAK shRNA-expressing line, nuclear factor-kappaB (NF-kappaB) was localized to the nucleus, but in the IRAK4 shRNA line, NF-kappaB levels were increased but the extent of nuclear localization was unchanged. Dominant negative mutants of IRAK4 and GAK also showed strong apoptotic effects in A498 cells under anoxia, supporting a direct link between these kinases and survival of the VHL-/- RCC line, which is typically highly resistant to hypoxic stress as a result of high and constitutive levels of Hif-1alpha.

[187]

**TÍTULO / TITLE:** - Impact of C-Reactive Protein on Prognosis of patients with Colorectal Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatogastroenterology. 2013 May 1;60(123). doi: 10.5754/hge11425.

●●Enlace al texto completo (gratis o de pago) [5754/hge11425](#)

**AUTORES / AUTHORS:** - Takasu C; Shimada M; Kurita N; Iwata T; Nishioka M; Morimoto S; Yoshikawa K; Miyatani T; Kashihara H

**RESUMEN / SUMMARY:** - :Background/Aims: The aim of this study was to investigate the impact of preoperative serum C-reactive protein (CRP) level as a prognostic indicator in patients with colorectal carcinoma (CRC). Methodology: We investigated the correlation between preoperative CRP level and clinicopathological factors including prognosis of 167 patients who underwent resection for CRC retrospectively. Clinicopathological variables were compared between patients with serum CRP levels >1mg/dL (29 patients; high-CRP group) and patients with serum CRP levels <1mg/dL (138 patients; low-CRP group). Results: In high-CRP group, 9 patients were stage I+II and 20 patients were stage III+IV. In low-CRP group, 93 patients were stage I+II and 45 patients were stage III+IV. There were significant differences in the clinical stage, tumor diameter, curativity, final stage between the two groups ( $p < 0.01$ ). The overall survival and recurrence-free survival rates in high-CRP group were lower compared with the rates in low-CRP group ( $p < 0.05$  and  $p = 0.14$ ). In addition, the overall survival rate in stage I+II patients with high-CRP was significantly lower than that in patients with low-CRP ( $p < 0.05$ ). Using multivariate analysis, the preoperative elevation of serum CRP level was an independent prognostic factor in patients with CRC ( $p < 0.05$ ). Conclusions: We found that the preoperative elevation of serum CRP to be an independent prognostic indicator of CRC.

[188]

**TÍTULO / TITLE:** - Feasibility and dose discovery analysis of zoledronic acid with concurrent chemotherapy in the treatment of newly diagnosed metastatic osteosarcoma: A report from the Children's Oncology Group.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Jul;49(10):2384-91. doi: 10.1016/j.ejca.2013.03.018. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.03.018](#)

**AUTORES / AUTHORS:** - Goldsby RE; Fan TM; Villaluna D; Wagner LM; Isakoff MS; Meyer J; Lor Randall R; Lee S; Kim G; Bernstein M; Gorlick R; Krailo M; Marina N

**INSTITUCIÓN / INSTITUTION:** - University of California San Francisco, Benioff Children's Hospital, San Francisco, CA, United States. Electronic address: [goldsbysr@pediatrics.ucsf.edu](mailto:goldsbysr@pediatrics.ucsf.edu).

**RESUMEN / SUMMARY:** - AIM: Patients with metastatic osteosarcoma (OS) have a poor outcome with conventional therapies. Zoledronic acid (ZA) is a third-generation bisphosphonate that reduces skeletal-related events in many adult cancers, and pre-clinical data suggest a possible benefit in OS. This study assessed the maximum tolerated dose (MTD) and the feasibility of ZA when combined with chemotherapy in patients with metastatic OS. PATIENTS AND METHODS: Patients with a histological diagnosis of OS were eligible if they were <40 years of age, had initially metastatic disease and met organ function requirements. Treatment combined surgery and a conventional chemotherapy regimen. ZA was given concurrent with chemotherapy for a total of eight doses over 36 weeks. Three dose levels of ZA were tested: 1.2mg/m<sup>2</sup> [max 2mg], 2.3mg/m<sup>2</sup> [max 4mg] and 3.5mg/m<sup>2</sup> [max 6mg]. The MTD was determined during induction. Six patients were to be treated at each dose level, with an additional six patients treated with the MTD to help assess post-induction feasibility. RESULTS: Twenty-four patients (median age 13.5 years [range, 7-22]; 16 females) were treated. Five patients experienced dose-limiting toxicities (DLTs) during induction, including three patients treated with 3.5mg/m<sup>2</sup>. DLTs included hypophosphatemia, hypokalemia, hyponatremia, mucositis, limb pain and limb oedema. There were no reports of excessive renal toxicity or osteonecrosis of the jaw. The MTD was defined as 2.3mg/m<sup>2</sup> (max 4mg). CONCLUSIONS: ZA can be safely combined with conventional chemotherapy with an MTD of 2.3mg/m<sup>2</sup> (max 4mg) for patients with metastatic osteosarcoma.

[189]

**TÍTULO / TITLE:** - DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. 2013 Jun 1;73(11):3326-35. doi: 10.1158/0008-5472.CAN-12-3055. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-3055](http://1158/0008-5472.CAN-12-3055)

**AUTORES / AUTHORS:** - Cao J; Song Y; Bi N; Shen J; Liu W; Fan J; Sun G; Tong T; He J; Shi Y; Zhang X; Lu N; He Y; Zhang H; Ma K; Luo X; Lv L; Deng H; Cheng J; Zhu J; Wang L; Zhan Q

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: State Key Laboratory of Molecular Oncology; Departments of Radiation Oncology, Thoracic Surgery, Medical Oncology, and Pathology, Cancer Hospital and Cancer Institute, Chinese Academy of Medical Sciences & Peking Union Medical College; National Engineering Research Center for Biochip Technology, Beijing;

Shanghai Cancer Institute, Shanghai; and Cancer Epigenetic Laboratory, Anhui Cancer Hospital, Hefei, China.

**RESUMEN / SUMMARY:** - Small cell lung cancer (SCLC) is one of the most aggressive types of cancer, yet the pathologic mechanisms underlying its devastating clinical outcome remain elusive. In this report, we surveyed 924 miRNA (miR) for their expressions in the formalin-fixed paraffin-embedded specimens from 42 patients with SCLC, and found that the downregulated miR-886-3p is closely correlated with the shorter survival of SCLC. This correlation was validated with another 40 cases. It was further discovered that loss of miR-886-3p expression was mediated by DNA hypermethylation of its promoter in both cultured SCLC cells and tumor samples. Moreover, miR-886-3p potently repressed cell proliferation, migration, and invasion of NCI-H446 cell in cell culture via suppression of the expression of its target genes: PLK1 and TGF-beta1 at posttranscription levels. Forced upregulation of miR-886-3p greatly inhibited in vivo tumor growth, bone/muscle invasion, and lung metastasis of NCI-H446 cells. This newly identified miR-886-3p-PLK1/TGF-beta1 nexus that modulates SCLC aggression suggests that both loss of miR-886-3p expression and hypermethylation of the miR-886 promoter are the promising indicators for poor outcome of as well as new therapeutic targets for SCLC. Cancer Res; 73(11); 3326-35. ©2013 AACR.

[190]

**TÍTULO / TITLE:** - Evaluation of Mucin-1 protein and mRNA expression as prognostic and predictive markers after neoadjuvant chemotherapy for breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt162](#)

**AUTORES / AUTHORS:** - Sinn BV; von Minckwitz G; Denkert C; Eidtmann H; Darb-Esfahani S; Tesch H; Kronenwett R; Hoffmann G; Belau A; Thommsen C; Holzhausen HJ; Grasshoff ST; Baumann K; Mehta K; Dietel M; Loibl S

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Charite-Universitätsmedizin Berlin, Berlin.

**RESUMEN / SUMMARY:** - BACKGROUND: Mucin-1 (MUC1) is a promising antigen for the development of tumor vaccines. We evaluated the frequency of MUC1 expression and its impact on therapy response and survival after neoadjuvant chemotherapy for breast cancer. PATIENTS AND METHODS: Pre-treatment core biopsies of patients from the GeparTrio neoadjuvant trial (NCT 00544765) were evaluated for MUC1 by immunohistochemistry (IHC; N = 691) and quantitative RT-PCR (qRT-PCR; N = 286) from formalin-fixed paraffin-embedded (FFPE) samples. RESULTS: MUC1 protein and mRNA was detectable in the majority of cases and was associated with hormone-receptor-positive status (P < 0.001). High MUC1 protein and mRNA expression were

associated with lower probability of pathologic complete response ( $P = 0.017$  and  $P < 0.001$ ) and with longer patient survival ( $P = 0.03$  and  $P < 0.001$ ). In multivariable analysis, MUC1 protein and mRNA expression were independently predictive ( $P = 0.001$  and  $P < 0.001$ ). MUC1 protein and mRNA expression were independently prognostic for overall survival ( $P = 0.029$  and  $P = 0.015$ ). CONCLUSIONS: MUC1 is frequently expressed in breast cancer and detectable on mRNA and protein level from FFPE tissue. It provides independent predictive information for therapy response and survival after neoadjuvant chemotherapy. In clinical immunotherapy trials, MUC1 expression may serve as a predictive marker.

[191]

**TÍTULO / TITLE:** - A microRNA-135a/b binding polymorphism in CD133 confers decreased risk and favorable prognosis of lung cancer in Chinese by reducing CD133 expression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bqt181](#)

**AUTORES / AUTHORS:** - Cheng M; Yang L; Yang R; Yang X; Deng J; Yu B; Huang D; Zhang S; Wang H; Qiu F; Zhou Y; Lu J

**INSTITUCIÓN / INSTITUTION:** - The Institute for Chemical Carcinogenesis, The State Key Lab of Respiratory Disease, Guangzhou Medical University, 195 Dongfengxi Road, Guangzhou 510182, China.

**RESUMEN / SUMMARY:** - CD133 is a pivotal marker of cancer stem cells (CSCs) that is involved in tumorigenesis and cancer progression. Recent studies have identified CD133 to be a prognostic factor for cancer related with its expression and genetic variants. Here, we hypothesized that the single nucleotide polymorphisms (SNP) in CD133 may be associated with lung cancer risk and prognosis. Based on three independent case-control analyses with a total of 2,332 lung cancer cases and 2,457 controls, the gene-based association analysis with 13 polymorphisms of CD133 suggested that CD133 is a susceptible gene for lung cancer ( $P = 0.043$ ) and that the SNP rs2240688A>C in the 3'-untranslated region of CD133 is the most significant associated SNP with the risk of lung cancer ( $P = 0.020$ ); further analysis showed that the rs2240688C variant genotypes (CA+CC) harbored a decreased risk of lung cancer (OR = 0.80; 95%CI= 0.72-0.90) and conferred a favorable survival for lung cancer patients (median survival time, MST: 15 months) when compared to AA genotype (MST: 11 months, log-rank test:  $P = 3.31 \times 10^{-6}$ ; Cox model: HR = 0.81, 95%CI = 0.70-0.94). Functional assays revealed that the rs2240688A to C transition gained a new binding of the microRNA hsa-miR-135a/b and decreased the CD133 expression. Our data suggest that the functional polymorphism rs2240688A>C in CD133 is associated with lung cancer risk and

survival. This SNP may be a functional biomarker to predict risk and prognosis of lung cancer.

[192]

**TÍTULO / TITLE:** - Phase I study of oral gemcitabine prodrug (LY2334737) in Japanese patients with advanced solid tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Jun;71(6):1645-55. doi: 10.1007/s00280-013-2165-2. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2165-](http://1007/s00280-013-2165-2)

[2](#)

**AUTORES / AUTHORS:** - Yamamoto N; Nokihara H; Yamada Y; Uenaka K; Sekiguchi R; Makiuchi T; Slapak CA; Benhadji KA; Tamura T

**INSTITUCIÓN / INSTITUTION:** - Division of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** - PURPOSE: LY2334737 is an oral gemcitabine prodrug. This Phase I study assessed the safety and tolerability of LY2334737 in Japanese patients with solid tumors and evaluated pharmacokinetics (PK), pharmacodynamics, and antitumor activity. METHODS: Patients with advanced/metastatic solid tumors received escalating doses of LY2334737 once daily for 14 days, followed by a 7-day drug-free period. Cycles were repeated until discontinuation criteria were met. RESULTS: Of 13 patients treated, 3 received 20 mg/day, 6 received 30 mg/day, 4 received 40 mg/day. On the 40 mg dose, 3 patients experienced dose-limiting toxicities (DLTs): hepatic toxicities (e.g., Grade [G]3/4 transaminase and G1-3 bilirubin elevation) and G4 thrombocytopenia; all 3 showed features of disseminated intravascular coagulation. One additional DLT occurred on the 30 mg dose (G3 transaminase elevation). Exploratory pharmacogenetic analyses identified a genetic variation in the CES2 gene potentially associated with these DLTs. PK data showed no clear relationship between the AUC of gemcitabine and its incorporation into leukocyte DNA; 2 of the 3 DLT patients had high incorporation. Two patients (30 mg/day) achieved stable disease with progression-free survival lasting 135 and 155 days. CONCLUSIONS: LY2334737 was tolerated by Japanese patients up to 30 mg/day. The toxicities observed at the 40 mg dose may require the development of alternative dosing schedules.

[193]

**TÍTULO / TITLE:** - Pregnane X receptor dependent up-regulation of CYP2C9 and CYP3A4 in tumor cells by antitumor acridine agents, C-1748 and C-1305, selectively diminished under hypoxia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Pharmacol. 2013 May 17. pii: S0006-2952(13)00292-X. doi: 10.1016/j.bcp.2013.05.008.

●●Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.05.008](http://1016/j.bcp.2013.05.008)

**AUTORES / AUTHORS:** - Niemira M; Dastyh J; Mazerska Z

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Technology and Biochemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-233, Gdansk, Poland. Electronic address: [m.niemira@gmail.com](mailto:m.niemira@gmail.com).

**RESUMEN / SUMMARY:** - Induction of proteins involved in drug metabolism and in drug delivery has a significant impact on drug-drug interactions and on the final therapeutic effects. Two antitumor acridine derivatives selected for present studies, C-1748 (9-(2'-hydroxyethylamino)-4-methyl-1-nitroacridine) and C-1305 (5-dimethylaminopropylamino-8-hydroxy-triazoloacridinone), expressed high and low susceptibility to metabolic transformations with liver microsomes, respectively. In the current study, we examined the influence of these compounds on cytochrome P450 3A4 (CYP3A4) and 2C9 (CYP2C9) enzymatic activity and gene expression in HepG2 tumor cells. Luminescence and HPLC examination, real-time RT-PCR and western blot analyses along with transfection of pregnane X receptor (PXR) siRNA and CYP3A4 reporter gene assays were applied. We found that both compounds strongly induced CYP3A4 and CYP2C9 activity and expression as well as expression of UGT1A1 and MDR1 in a concentration- and time-dependent manner. C-1748-mediated CYP3A4 and CYP2C9 mRNA induction equal to rifampicin occurred at extremely low concentrations (0.001 and 0.01µM), whereas 10µM C-1305 induced three-times higher CYP3A4 and CYP2C9 mRNA levels than rifampicin did. CYP3A4 and CYP2C9 expressions were shown to be PXR-dependent; however, neither compound influenced PXR expression. Thus, the observed drug-mediated induction of isoenzymes occurs on a PXR-mediated regulatory level. Furthermore, C-1748 and C-1305 were demonstrated to be selective PXR agonists. These effects are hypoxia-inhibited only in the case of C-1748, which is sensitive to P450 metabolism. In summary, PXR was found to be a new target of the studied compounds. Thus, possible combinations of these compounds with other therapeutics might lead to the PXR-dependent enzyme-mediated drug-drug interactions.

[194]

**TÍTULO / TITLE:** - Serum levels of IL-6 and IL-1beta can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 May 28;108(10):2063-9. doi: 10.1038/bjc.2013.174. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.174](http://1038/bjc.2013.174)

**AUTORES / AUTHORS:** - Mitsunaga S; Ikeda M; Shimizu S; Ohno I; Furuse J; Inagaki M; Higashi S; Kato H; Terao K; Ochiai A

**INSTITUCIÓN / INSTITUTION:** - 1] Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan [2] Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan.

**RESUMEN / SUMMARY:** - Background:With this study, we sought to characterise the impact of pro-inflammatory cytokines on the outcomes of gemcitabine monotherapy (GEM) in patients with pancreatic cancer (PC).Methods:Treatment-naive patients with advanced PC and no obvious infections were eligible for enrolment. All of the patients were scheduled to undergo systemic chemotherapy. Serum pro-inflammatory cytokines were measured using an electro-chemiluminescence assay method before chemotherapy. High cytokine levels were defined as values greater than the median. Clinical data were collected prospectively.Results:Sixty patients who received GEM were included in the analysis. High IL-6 and IL-1beta levels were poor prognostic factors for overall survival in a multivariate analysis (P=0.011 and P=0.048, respectively). Patients with both a high IL-6 level and a high IL-1beta level exhibited shortened overall and progression-free survival, a reduction in the tumour control rate, and a high dose intensity of GEM compared with patients with low levels of both IL-6 and IL-1beta.Conclusion:The serum levels of IL-6 and IL-1beta predict the efficacy of GEM in patients with advanced PC.

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[195]

**TÍTULO / TITLE:** - Evodiamine induces apoptosis and inhibits metastasis in MDAMB-231 human breast cancer cells in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 May 27. doi: 10.3892/or.2013.2498.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2498](#)

**AUTORES / AUTHORS:** - Du J; Wang XF; Zhou QM; Zhang TL; Lu YY; Zhang H; Su SB

**INSTITUCIÓN / INSTITUTION:** - Research Center for Traditional Chinese Medicine Complexity System, Shanghai University of Traditional Chinese Medicine, Pudong, Shanghai 201203, P.R. China.

**RESUMEN / SUMMARY:** - Breast cancer remains the leading cause of cancer-related deaths among women. Owing to high efficiency and low toxic effects, further exploration of natural compounds from Chinese herbal medicine may be an efficient approach for breast cancer drug discovery. In this study, we investigated the effects of evodiamine on the growth and metastasis of MDA-MB-231 human breast cancer cells in vitro and in vivo. In vitro, evodiamine inhibited cell migration and invasion abilities through downregulation of MMP-9, urokinase-type plasminogen activator (uPA) and uPAR expression. Evodiamine-induced G0/G1 arrest and apoptosis were associated with a decrease in Bcl-2, cyclin D1 and cyclin-dependent kinase 6 (CDK6) expression

and an increase in Bax and p27Kip1 expression. Moreover, evodiamine regulated p-ERK and p-p38 MAPK expression. Evodiamine-induced apoptosis was enhanced by its combination with the extracellular signal-regulated kinase (ERK) inhibitor PD98059 or the p38 mitogen-activated protein kinase (p38 MAPK) inhibitor SB203580. Evodiamine-inhibited metastasis was partly blocked by combination with PD98059 or SB203580. In vivo, the administration of evodiamine (10 mg/kg) significantly reduced tumor growth and pulmonary metastasis. These results demonstrate that evodiamine possesses antitumor activities via inhibition of cell migration and invasion, arrest of the cell cycle and induction of cell apoptosis in MDA-MB-231 cells.

[196]

**TÍTULO / TITLE:** - Combined Neoadjuvant Chemotherapy With Bevacizumab Improves Pathologic Complete Response in Patients With Hormone Receptor Negative Operable or Locally Advanced Breast Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Clin Oncol. 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago)

[1097/COC.0b013e31828940c3](#)

**AUTORES / AUTHORS:** - Makhoul I; Klimberg VS; Korourian S; Henry-Tillman RS; Siegel ER; Westbrook KC; Hutchins LF

**INSTITUCIÓN / INSTITUTION:** - \*Hematology/Oncology Division Departments of Breast Surgical Oncology double Pathology section Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR.

**RESUMEN / SUMMARY:** - **OBJECTIVES:** To evaluate the pathologic complete response (pCR) and safety of bevacizumab (B) with chemotherapy in the neoadjuvant setting of breast cancer (BC). **METHODS:** A prospective single-arm, single-institution phase II trial for women with stage IIA-B/IIIA-B-C BC. Patients received neoadjuvant docetaxel, cyclophosphamide, B every 3 weeks for 4 cycles followed by doxorubicin every 3 weeks for 4 cycles followed by surgery. After healing, B was given every 3 weeks for 9 cycles. Radiation therapy, trastuzumab and endocrine therapy were given as indicated. **RESULTS:** Thirty-nine of 40 patients were evaluable. Median age of participants was 45 years (range, 26 to 72 y). The most serious grade  $\geq 3$  adverse events were infection (4), congestive heart failure (2), and pulmonary embolism (1). Thirty-eight of 39 patients underwent surgery. The pCR rate was 41% (16/39), significantly higher than the null-hypothesis rate of 25% ( $P=0.0204$ ). Rates of pCR were 52% (15/29) in ductal carcinoma compared with 10% (1/10) in nonductal disease ( $P=0.021$ ), and 59% (10/17) in estrogen receptor-/progesteron receptor- patients compared with 27% (6/22) among patient with at least one positive hormone receptor ( $P=0.047$ ). African Americans (AA) had 75% pCR (9/12), whereas Whites had only 28% pCR (7/25;  $P=0.0069$ ), possibly in part because 100% of AA (12/12) had ductal

carcinoma compared with only 64% (16/25) of Whites (P=0.017).

CONCLUSIONS:: Chemotherapy with B improved pCR in BC patients, but was associated with significant toxicity and rare but very serious complications. The improvement was more pronounced in AA patients, those with ductal carcinoma, and those with estrogen receptor-/progesteron receptor - BC.ClinicalTrials.gov Identifier: NCT00203502.

[197]

**TÍTULO / TITLE:** - Risk of liver toxicity with the angiogenesis inhibitor pazopanib in cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Oncol. 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago)

[3109/0284186X.2013.782103](#)

**AUTORES / AUTHORS:** - Kapadia S; Hapani S; Choueiri TK; Wu S

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Oncology, Department of Medicine, Stony Brook University School of Medicine , Stony Brook, New York , USA.

**RESUMEN / SUMMARY:** - Purpose. The angiogenesis inhibitor pazopanib has been approved for the treatment of advanced renal cell cancer (RCC) and soft tissue sarcoma. Severe and fatal hepatotoxicity has been observed in its clinical studies. This analysis was conducted to determine the risk of liver toxicity by a systematic review and meta-analysis of clinical trials. Patients and methods. Databases from PubMed, Web of Science and abstracts presented at ASCO meetings up to January, 2012 were searched to identify relevant studies. Eligible studies included prospective trials of cancer patients treated with pazopanib starting at 800 mg daily. Summary incidence rates, relative risks, and 95% confidence intervals (CIs) were calculated using a fixed- or random-effects model. Results. A total of 1478 patients from 10 clinical trials were included. The incidences of all-grade aspartate aminotransferase (AST), alanine transaminase (ALT), and bilirubin elevation were 39.6% (95% CI 31.2-48.6%), 41.4% (95% CI 34.1-49.0%), and 24.8% (95% CI 16.3-35.3%), respectively. The incidences of high-grade (Grade 3 and 4) AST, ALT and bilirubin elevation were 6.9% (95% CI 5.5-8.6%), 9.4% (95% CI 7.8-11.4%), and 3.4% (2.4-5.0%), respectively. In comparison with placebo, pazopanib significantly increased the risk of high-grade AST elevation (RR 6.56, 95% CI 2.04-21.07, p = 0.002) and ALT elevation (RR 4.33, 95% CI 1.88-10.0, p = 0.001). However, the risks of high-grade bilirubin elevation (RR 1.31, 95% CI 0.47-3.64) and fatal hepatotoxicity (RR 2.51, 95% CI 0.12-51.91, p = 0.55) were not significantly elevated. Conclusion. The use of pazopanib was associated with a significantly increased risk of severe non-fatal hepatotoxicity in cancer patients.

[198]

**TÍTULO / TITLE:** - Fulvestrant regulates epidermal growth factor (EGF) family ligands to activate EGF receptor (EGFR) signaling in breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):351-60. doi: 10.1007/s10549-013-2541-y. Epub 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2541-](#)

[y](#)

**AUTORES / AUTHORS:** - Zhang X; Diaz MR; Yee D

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Masonic Cancer Center, University of Minnesota, MMC 806, 420 Delaware Street SE, Minneapolis, MN, 55455, USA.

**RESUMEN / SUMMARY:** - Estrogen receptor-alpha (ER) targeted therapies are routinely used to treat breast cancer. However, patient responses are limited by resistance to endocrine therapy. Breast cancer cells resistant to the pure steroidal ER antagonist fulvestrant (fulv) demonstrate increased activation of epidermal growth factor receptor (EGFR) family members and downstream ERK signaling. In this study, we investigated the effects of fulv on EGFR signaling and ligand regulation in several breast cancer cell lines. EGFR/HER2/HER3 phosphorylation and ERK1,2 activation were seen after 24-48 h after fulvestrant treatment in ER-positive breast cancer cell lines. 4-Hydroxy-tamoxifen and estradiol did not cause EGFR activation. Fulvestrant did not affect EGFR expression. Cycloheximide abolished the ability of fulv to activate EGFR suggesting the autocrine production of EGFR ligands might be responsible for fulvestrant induced EGFR signaling. qRT-PCR results showed fulv differentially regulated EGFR ligands; HB-EGF mRNA was increased, while amphiregulin and epiregulin mRNAs were decreased. Fulvestrant induced EGFR activation and upregulation of EGFR ligands were ER dependent since fulv treatment in C4-12, an ER-negative cell line derivative of MCF-7 cells, did not result in EGFR activation or change in ligand mRNA levels. ER downregulation by siRNA induced similar EGFR activation and regulation of EGFR ligands as fulvestrant. Neutralizing HB-EGF antibody blocked fulv-induced EGFR activation. Combination of fulv and EGFR family tyrosine kinase inhibitors (erlotinib and lapatinib) significantly decreased EGFR signaling and cell survival. In conclusion, fulvestrant-activated EGFR family members accompanied by ER dependent upregulation of HB-EGF within 48 h. EGF receptor or ligand inhibition might enhance or prolong the therapeutic effects of targeting ER by fulvestrant in breast cancer.

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[199]

**TÍTULO / TITLE:** - Evaluating the performance of the breast cancer genetic risk models BOADICEA, IBIS, BRCAPRO and Claus for predicting BRCA1/2

mutation carrier probabilities: a study based on 7352 families from the German Hereditary Breast and Ovarian Cancer Consortium.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Genet. 2013 Jun;50(6):360-7. doi: 10.1136/jmedgenet-2012-101415. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1136/jmedgenet-2012-101415](#)

**AUTORES / AUTHORS:** - Fischer C; Kuchenbacker K; Engel C; Zachariae S; Rhiem K; Meindl A; Rahner N; Dikow N; Plendl H; Debatin I; Grimm T; Gadzicki D; Flottmann R; Horvath J; Schrock E; Stock F; Schafer D; Schwaab I; Kartsonaki C; Mavaddat N; Schlegelberger B; Antoniou AC; Schmutzler R

**INSTITUCIÓN / INSTITUTION:** - Institute of Human Genetics, University of Heidelberg, Im Neuenheimer Feld 366, Heidelberg 69120, Germany; [cfischer@uni-hd.de](mailto:cfischer@uni-hd.de).

**RESUMEN / SUMMARY:** - BACKGROUND: Risk prediction models are widely used in clinical genetic counselling. Despite their frequent use, the genetic risk models BOADICEA, BRCAPRO, IBIS and extended Claus model (eCLAUS), used to estimate BRCA1/2 mutation carrier probabilities, have never been comparatively evaluated in a large sample from central Europe. Additionally, a novel version of BOADICEA that incorporates tumour pathology information has not yet been validated. PATIENTS AND METHODS: Using data from 7352 German families we estimated BRCA1/2 carrier probabilities under each model and compared their discrimination and calibration. The incremental value of using pathology information in BOADICEA was assessed in a subsample of 4928 pedigrees with available data on breast tumour molecular markers oestrogen receptor, progesterone receptor and human epidermal growth factor 2. RESULTS: BRCAPRO (area under receiver operating characteristic curve (AUC)=0.80 (95% CI 0.78 to 0.81)) and BOADICEA (AUC=0.79 (0.78-0.80)), had significantly higher diagnostic accuracy than IBIS and eCLAUS ( $p<0.001$ ). The AUC increased when pathology information was used in BOADICEA: AUC=0.81 (95% CI 0.80 to 0.83,  $p<0.001$ ). At carrier thresholds of 10% and 15%, the net reclassification index was +3.9% and +5.4%, respectively, when pathology was included in the model. Overall, calibration was best for BOADICEA and worst for eCLAUS. With eCLAUS, twice as many mutation carriers were predicted than observed. CONCLUSIONS: Our results support the use of BRCAPRO and BOADICEA for decision making regarding genetic testing for BRCA1/2 mutations. However, model calibration has to be improved for this population. eCLAUS should not be used for estimating mutation carrier probabilities in clinical settings. Whenever possible, breast tumour molecular marker information should be taken into account.

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[200]

**TÍTULO / TITLE:** - Do acetylcholine receptor and striated muscle antibodies predict the presence of thymoma in patients with myasthenia gravis?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Muscle Nerve. 2013 Apr 27. doi: 10.1002/mus.23882.

●●Enlace al texto completo (gratis o de pago) [1002/mus.23882](#)

**AUTORES / AUTHORS:** - Decroos EC; Hobson-Webb LD; Juel VC; Massey JM; Sanders DB

**INSTITUCIÓN / INSTITUTION:** - Neuromuscular Section, Division of Neurology, Department of Medicine, Duke University Medical Center, Durham, NC, USA.

**RESUMEN / SUMMARY:** - Introduction: Acetylcholine receptor (AChR) and striated muscle antibodies (StrAbs) are frequently found in myasthenia gravis (MG) patients with thymoma. This study aimed to determine the positive (PPV) and negative predictive value (NPV) of these antibodies for thymoma in patients with MG. Methods: Antibody findings, thymic histology, and onset age were reviewed for 1141 patients with MG. PPV and NPV of these antibodies for thymoma were determined. Results: The PPV of AChR binding antibodies plus StrAbs was highest (50.0%) with onset before age 40. The PPV of all antibodies was low (<9%) after age 40. Higher StrAb levels did not increase the PPV. The NPV of AChR binding antibodies was high (99.7%) for all ages. Conclusion: Patients without AChR binding antibody are unlikely to have a thymoma. StrAbs and AChR binding antibodies are not diagnostic for thymoma, but in early onset MG, their presence should raise the clinical suspicion for thymoma. © 2013 Wiley Periodicals, Inc.

[201]

**TÍTULO / TITLE:** - The mRNA expression of inhibitors of DNA binding-1 and -2 is associated with advanced tumour stage and adverse clinical outcome in human breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):2179-83.

**AUTORES / AUTHORS:** - Wazir U; Jiang WG; Sharma AK; Newbold RF; Mokbel K

**INSTITUCIÓN / INSTITUTION:** - London Breast Institute, the Princess Grace Hospital, 45 Nottingham Place, London W1U 5NY, U.K.

[kefahmokbel@hotmail.com](mailto:kefahmokbel@hotmail.com).

**RESUMEN / SUMMARY:** - Inhibitors of DNA binding (ID) are known to have a role in embryogenesis and oncogenesis. In this study, we analyzed the role of ID1 and ID2 in breast cancer, by assessing associations of mRNA expression with clinicopathological parameters. MATERIALS AND METHODS: Breast cancer tissues (n=152) and adjacent normal tissues (n=31) underwent reverse transcription and quantitative- polymerase chain reaction (qPCR). Transcript levels were correlated with clinicopathological data. RESULTS: Patients who were disease-free had significantly lower ID1 mRNA expression than all other patients (p=0.0033). Higher expression was associated with worse disease-free

( $p=0.001$ ) and overall survival ( $p=0.02$ ). ID2 expression was directly associated with the Nottingham Prognostic Index (NPI) (NPI 2 vs. 3;  $p=0.0062$ ) and worsening clinical outcome (disease-free vs. mortality:  $p=0.0004$ ), and with worse disease-free ( $p=0.01$ ) and overall survival ( $p=0.005$ ). CONCLUSION: Our findings are suggestive of a role for ID1 and ID2 in human breast cancer as possible prognostic markers and therapeutic targets meriting further validating investigations, by immunohistochemistry and mechanistic studies.

[202]

**TÍTULO / TITLE:** - An anthraquinone derivative, emodin sensitizes hepatocellular carcinoma cells to TRAIL induced apoptosis through the induction of death receptors and downregulation of cell survival proteins.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Apoptosis. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1007/s10495-013-0851-](#)

[5](#)

**AUTORES / AUTHORS:** - Subramaniam A; Loo SY; Rajendran P; Manu KA; Perumal E; Li F; Shanmugam MK; Siveen KS; Park JI; Ahn KS; Hui KM; Kumar AP; Sethi G

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 117597, Singapore.

**RESUMEN / SUMMARY:** - Recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is currently under clinical trials for cancer, however many tumor cells, including hepatocellular carcinoma (HCC) develop resistance to TRAIL-induced apoptosis. Hence, novel agents that can alleviate TRAIL-induced resistance are urgently needed. In the present report, we investigated the potential of emodin to enhance apoptosis induced by TRAIL in HCC cells. As observed by MTT cytotoxicity assay and the externalization of the membrane phospholipid phosphatidylserine, we found that emodin can significantly potentiate TRAIL-induced apoptosis in HCC cells. When investigated for the mechanism(s), we observed that emodin can downregulate the expression of various cell survival proteins, and induce the cell surface expression of both TRAIL receptors, death receptors (DR) 4 as well as 5. In addition, emodin increased the expression of C/EBP homologous protein (CHOP) in a time-dependent manner. Knockdown of CHOP by siRNA decreased the induction of emodin-induced DR5 expression and apoptosis. Emodin-induced induction of DR5 was mediated through the generation of reactive oxygen species (ROS), as N-acetylcysteine blocked the induction of DR5 and the induction of apoptosis. Also, the knockdown of X-linked inhibitor of apoptosis protein by siRNA significantly reduced the sensitization effect of emodin on TRAIL-induced apoptosis. Overall, our experimental results clearly indicate that emodin can indeed potentiate TRAIL-induced apoptosis through

the downregulation of antiapoptotic proteins, increased expression of apoptotic proteins, and ROS mediated upregulation of DR in HCC cells.

[203]

**TÍTULO / TITLE:** - Erratum to: Thrombocytosis and immunohistochemical expression of connexin 43 at diagnosis predict survival in advanced non-small-cell lung cancer treated with cisplatin-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2188-](#)

[8](#)

**AUTORES / AUTHORS:** - Du G; Yang Y; Zhang Y; Sun T; Liu W; Wang Y; Li J; Zhang H

**INSTITUCIÓN / INSTITUTION:** - Institute of Pharmacy, Pharmacy College of Henan University, Jinming street, Kaifeng, 475004, Henan, China, [kfdgj@sohu.com](mailto:kfdgj@sohu.com).

[204]

**TÍTULO / TITLE:** - Impact of NOD2 polymorphisms on infectious complications following chemotherapy in patients with acute myeloid leukaemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1734-](#)

[0](#)

**AUTORES / AUTHORS:** - Yomade O; Spies-Weissart B; Glaser A; Schnetzke U; Hochhaus A; Scholl S

**INSTITUCIÓN / INSTITUTION:** - Abteilung Hamatologie/Internistische Onkologie, Klinik für Innere Medizin II, Jena University Hospital, Erlanger Allee 101, 07740, Jena, Germany.

**RESUMEN / SUMMARY:** - We sought to investigate the relationship between polymorphisms of the NOD2 gene and infectious complications following intensive induction chemotherapy in patients with acute myeloid leukaemia (AML). We hypothesised that single nucleotide polymorphisms (SNPs) of the NOD2 gene are associated with a higher rate of infections during the phase of severe neutropenia. In 131 AML patients receiving induction therapy, the presence of the three most frequent polymorphisms of NOD2 (Arg702Trp, Gly908Arg, Leu1007fsinsC) was analysed. SNP analyses by means of genomic PCR incorporating fluorescence-labelled probes with characteristic melting curves were performed using the LightCycler platform. Our data suggest a significantly lower probability of mucositis or enteritis in AML patients lacking any of the three evaluated NOD2 polymorphisms. Furthermore, bloodstream cultures of AML patients carrying either a missense or a frameshift mutation of NOD2 were significantly more frequently tested positive concerning

Streptococcus spp. In contrast, the presence of NOD2 polymorphisms had no impact on such important infectious complications as systemic inflammatory response syndrome or sepsis, the rate of central venous catheter infections or the incidence of pneumonia including fungal infections. Our data represent one of the first reports investigating the impact of polymorphisms of the innate immune system on infectious complications in patients with neutropenia following chemotherapy. A correlation between NOD2 polymorphisms and infectious events in AML patients is demonstrated.

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[205]

**TÍTULO / TITLE:** - A Phase I first-in-human study with tefinostat - a monocyte/macrophage targeted histone deacetylase inhibitor - in patients with advanced haematological malignancies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Haematol. 2013 May 7. doi: 10.1111/bjh.12359.

●●Enlace al texto completo (gratis o de pago) [1111/bjh.12359](#)

**AUTORES / AUTHORS:** - Ossenkoppele GJ; Lowenberg B; Zachee P; Vey N; Breems D; Van de Loosdrecht AA; Davidson AH; Wells G; Needham L; Bawden L; Toal M; Hooffman L; Debnam PM

**INSTITUCIÓN / INSTITUTION:** - Department of Haematology, VU University Medical Centre, Amsterdam, The Netherlands.

**RESUMEN / SUMMARY:** - Tefinostat (CHR-2845) is a monocyte/macrophage targeted histone deacetylase inhibitor (HDACi). This first-in-human, standard 3 + 3 dose escalating trial of oral, once daily tefinostat was conducted to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profile of tefinostat in relapsed/refractory haematological diseases. Eighteen patients were enrolled at doses of 20-640 mg. Plasma concentrations of tefinostat exceeded those demonstrated to give in vitro anti-proliferative activity. Flow cytometric pharmacodynamic assays demonstrated monocyte-targeted increases in protein acetylation, without corresponding changes in lymphocytes. Dose-limiting toxicities (DLTs) were not observed and dose escalation was halted at 640 mg without identification of the maximum tolerated dose. Drug-related toxicities were largely Common Toxicity Criteria for Adverse Events grade ½ and included nausea, anorexia, fatigue, constipation, rash and increased blood creatinine. A patient with chronic monomyelocytic leukaemia achieved a bone marrow response, with no change in peripheral monocytes. An acute myeloid leukaemia type M2 patient showed a >50% decrease in bone marrow blasts and clearance of peripheral blasts. In conclusion, tefinostat produces monocyte-targeted HDACi activity and is well tolerated, without the DLTs, e.g. fatigue, diarrhoea, thrombocytopenia, commonly seen with non-targeted HDACi. The early signs of efficacy and absence of significant toxicity warrant further evaluation of tefinostat in larger studies. (clinicaltrials.gov identifier: NCT00820508).

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[206]

**TÍTULO / TITLE:** - Rare, Germline Mutation of KIT With Imatinib-Resistant Multiple GI Stromal Tumors and Mastocytosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Jun 1;31(16):e245-7. doi: 10.1200/JCO.2012.42.0133. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1200/JCO.2012.42.0133](#)

**AUTORES / AUTHORS:** - Speight RA; Nicolle A; Needham SJ; Verrill MW; Bryon J; Panter S

**INSTITUCIÓN / INSTITUTION:** - MA (Cantab), MBBS (Hons), Department of Gastroenterology, RVI, Queen Victoria Rd, Newcastle upon Tyne, NE1 4LP, United Kingdom; [Allyspeight@doctors.org.uk](mailto:Allyspeight@doctors.org.uk).

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[207]

**TÍTULO / TITLE:** - Salvage-targeted kidney cancer therapy in patients progressing on high-dose interleukin-2 immunotherapy: the UCLA experience.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer J. 2013 May-Jun;19(3):189-96. doi: 10.1097/PPO.0b013e318292e8a4.

●●Enlace al texto completo (gratis o de pago)

[1097/PPO.0b013e318292e8a4](#)

**AUTORES / AUTHORS:** - Birkhauser FD; Pantuck AJ; Rampersaud EN; Wang X; Kroeger N; Pouliot F; Zomorodian N; Riss J; Li G; Kabbinar FF; Belldegrun AS

**INSTITUCIÓN / INSTITUTION:** - From the \*Institute of Urologic Oncology, David Geffen School of Medicine, University of California, Los Angeles, CA; daggerDepartment of Urology, University of Bern, Switzerland; and double daggerDepartment of Biostatistics, School of Public Health, University of California, Los Angeles, CA.

**RESUMEN / SUMMARY:** - PURPOSE: To analyze the outcomes of patients with metastatic renal cell carcinoma treated with salvage-targeted therapy after progressing on high-dose interleukin (IL)-2 immunotherapy in a tertiary referral center. MATERIALS AND METHODS: A retrospective nonrandomized cohort consisting of 286 patients with metastatic renal cell carcinoma treated from 2003 to 2010 was analyzed from the University of California, Los Angeles (UCLA) Kidney Cancer database. All patients underwent cytoreductive nephrectomy, and 21 patients received salvage-targeted therapy after progression on high-dose IL-2, whereas 111 patients received targeted therapy alone. The remaining 154 patients had other treatment combinations or experimental targeted therapy agents only. Since 2003, selection of patients for high-dose IL-2 was increasingly based on clinical, pathologic, and molecular

criteria (UCLA CPM criteria). Disease-specific survival was calculated from diagnosis of metastatic renal cell carcinoma. RESULTS: Patients selected according to UCLA CPM criteria and treated with salvage-targeted therapy after progressing on high-dose IL-2 experienced a significantly greater disease-specific survival (median not reached) than those treated with targeted therapy alone (30 months; P = 0.004). Since 2006, all high-dose IL-2 patients met the UCLA CPM criteria and were able to receive salvage-targeted therapy upon progression. Disease-specific survival calculated from initiation of targeted therapy was comparable for patients treated with salvage-targeted therapy after progression on high-dose IL-2 (34 months) versus first-line targeted therapy (26 months; P = 0.175). DISCUSSION: Patients selected for high-dose IL-2 based on UCLA CPM criteria and treated with salvage-targeted therapy upon progression have achieved outstanding disease-specific survival. Our data suggest a new algorithm for carefully selected patients with metastatic renal cell carcinoma based on UCLA CPM criteria to receive first-line high-dose IL-2 while reserving their option for salvage-targeted therapy with uncompromised efficacy upon progression.

[208]

**TÍTULO / TITLE:** - Is interleukin 2 the best initial therapy for many patients with metastatic renal cell carcinoma?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer J. 2013 May-Jun;19(3):197-8. doi: 10.1097/PPO.0b013e318292e6a2.

●●Enlace al texto completo (gratis o de pago)

[1097/PPO.0b013e318292e6a2](#)

**AUTORES / AUTHORS:** - Philips G; Atkins MB

**INSTITUCIÓN / INSTITUTION:** - From the Departments of Oncology and Medicine, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC.

[209]

**TÍTULO / TITLE:** - Incorporation of 6-thioguanine nucleotides into DNA during maintenance therapy of childhood acute lymphoblastic leukemia-the influence of thiopurine methyltransferase genotypes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Pharmacol. 2013 Jun;53(6):670-4. doi: 10.1002/jcph.81. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago) [1002/jcph.81](#)

**AUTORES / AUTHORS:** - Ebbesen MS; Nersting J; Jacobsen JH; Frandsen TL; Vettenranta K; Abramsson J; Wesenberg F; Schmiegelow K

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics and Adolescent Medicine, The University Hospital Rigshospitalet, Copenhagen, Denmark.

[210]

**TÍTULO / TITLE:** - Effects of cyclophosphamide and IL-2 on regulatory CD4(+) T cell frequency and function in melanoma patients vaccinated with HLA-class I peptides: impact on the antigen-specific T cell response.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Immunol Immunother. 2013 May;62(5):897-908. doi: 10.1007/s00262-013-1397-7. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1007/s00262-013-1397-](#)

[7](#)

**AUTORES / AUTHORS:** - Camisaschi C; Filipazzi P; Tazzari M; Casati C; Beretta V; Pilla L; Patuzzo R; Maurichi A; Cova A; Maio M; Chiarion-Sileni V; Tragni G; Santinami M; Vergani B; Villa A; Berti E; Umansky L; Beckhove P; Umansky V; Parmiani G; Rivoltini L; Castelli C

**INSTITUCIÓN / INSTITUTION:** - Unit of Immunotherapy of Human Tumors, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian 1, 20133, Milan, Italy.

**RESUMEN / SUMMARY:** - The frequency and function of regulatory T cells (Tregs) were studied in stage II-III melanoma patients who were enrolled in a phase II randomized trial of vaccination with HLA-A\*0201-modified tumor peptides versus observation. The vaccinated patients received low-dose cyclophosphamide (CTX) and low-dose interleukin-2 (IL-2). Tregs were analyzed in the lymph nodes (LNs) of stage III patients who were undergoing complete lymph node dissection and in peripheral blood mononuclear cells (PBMCs) collected before vaccination and at different time points during the vaccination period. The LNs of the vaccinated patients, which were surgically removed after two rounds of vaccination and one dose of CTX, displayed a low frequency of Tregs and a less immunosuppressive environment compared with those of the untreated patients. The accurate time-course analysis of the PBMCs of patients enrolled in the vaccination arm indicated a limited and transient modulation in the frequencies of Tregs in PBMCs collected after low-dose CTX administration and a strong Treg boost in those PBMCs collected after low-dose IL-2 administration. However, a fraction of the IL-2-boosted Tregs was functionally modulated to a Th-1-like phenotype in the vaccinated patients. Moreover, low-dose IL-2 promoted the concomitant expansion of conventional activated CD4(+) T cells. Despite the amplification of Tregs, IL-2 administration maintained or further increased the number of antigen-specific CD8(+) T cells that were induced by vaccination as demonstrated by the ex vivo human leukocyte antigen-multimer staining and IFN-gamma ELISpot assays. Our study suggests that the use of CTX as a Treg modulator should be revised in terms of the administration schedule and of patients who may benefit from this drug treatment. Despite the Treg expansion that was observed in this study, low-dose IL-2 is not detrimental to the functional activities of vaccine-primed

CD8(+) T cell effectors when used in the inflammatory environment of vaccination.

[211]

**TÍTULO / TITLE:** - High pretreatment serum lactate dehydrogenase level correlates with disease relapse and predicts an inferior outcome in locally advanced nasopharyngeal carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Jul;49(10):2356-64. doi: 10.1016/j.ejca.2013.03.008. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.03.008](http://1016/j.ejca.2013.03.008)

**AUTORES / AUTHORS:** - Wan XB; Wei L; Li H; Dong M; Lin Q; Ma XK; Huang PY; Wen JY; Li X; Chen J; Ruan DY; Lin ZX; Chen ZH; Liu Q; Wu XY; Hong MH

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

**RESUMEN / SUMMARY:** - **PURPOSE:** Here, we evaluate the prognostic effect of pretreatment serum lactate dehydrogenase (LDH) in locally advanced nasopharyngeal carcinoma (NPC). **METHODS AND MATERIALS:** Pretreatment serum samples from a randomized controlled trial, which contained 199 neoadjuvant chemoradiotherapy patients and 201 neoadjuvant-concurrent chemoradiotherapy cases with locally advanced NPC, were collected and examined for LDH. With 5-year follow-up, the prognostic effect of pretreatment serum LDH was analysed by Kaplan-Meier analysis and multivariate Cox regression model. **RESULTS:** Three hundred and sixty-seven patients (91.75%) had a normal (109.0-245.0U/L) pretreatment LDH level, compared to 33 cases (8.25%) that had a higher (245.0U/L) LDH level. The mean and median pretreatment LDH levels of these 400 patients were 186.6 and 174.0U/L (range, 83.0-751.0U/L), respectively. Compared with the normal subset, elevated LDH level predicted an inferior 5-year overall survival (56.9% versus 76.8%, P=0.004), disease-free survival (DFS, 45.4% versus 64.7%, P=0.001), local relapse-free survival (76.1% versus 89.6%, P=0.019) and distant metastasis-free survival (DMFS, 54.3% versus 72.2%, P=0.001). Multivariate analysis confirmed that the LDH level was an independent prognostic factor to predict death, disease progression, local relapse and distant metastasis. For the subgroup with normal LDH (median point of 177.0U/L), we detected an evident 5-year DFS (68.8% versus 59.5%, P=0.047) and DMFS advantage (77.3% versus 65.3%, P=0.016) in 109.0-177.0U/L subset than that of 178.0-245.0U/L subgroup. **CONCLUSIONS:** Serological LDH level was an independent prognostic factor for locally advanced NPC. Combining pretreatment LDH with TNM staging might lead to more accurate risk definition.

[212]

**TÍTULO / TITLE:** - Troglitazone, a thiazolidinedione, decreases tau phosphorylation through the inhibition of cyclin-dependent kinase 5 activity in SH-SY5Y neuroblastoma cells and primary neurons.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurochem. 2013 Apr 13. doi: 10.1111/jnc.12264.

●●Enlace al texto completo (gratis o de pago) [1111/jnc.12264](#)

**AUTORES / AUTHORS:** - Cho DH; Lee EJ; Kwon KJ; Shin CY; Song KH; Park JH; Jo I; Han SH

**INSTITUCIÓN / INSTITUTION:** - Department of Neurology, Konkuk University Medical Center, Konkuk University, Seoul, South Korea; Department of Pharmacology, Center for Geriatric Neuroscience Research, SMART Institute of Advanced Biomedical Science School of Medicine, Konkuk University, Seoul, South Korea.

**RESUMEN / SUMMARY:** - The peroxisome proliferator-activated receptor gamma (PPARgamma) agonists thiazolidinediones (TZDs) are prescribed for the treatment of type 2 diabetes mellitus. Furthermore, it has been reported that TZDs have a beneficial effect on neurodegenerative disorders, such as Alzheimer's disease. However, the molecular mechanisms underlying this effect are not fully understood. Here, we investigated whether and how troglitazone, a parent TZD drug, inhibits tau phosphorylation. Treatment with troglitazone decreased tau-Thr231 phosphorylation and p35, the specific activator of cyclin-dependent kinase 5 (CDK5), in a dose- and time-dependent manner. Troglitazone also decreased CDK5 enzymatic activity, and ectopic expression of p25, the cleaved and more active form of p35, restored the troglitazone-induced decrease in tau-Thr231 phosphorylation. Treatment with either MG-132, a reversible proteasome inhibitor, or lactacystin, a specific and irreversible 26S proteasome inhibitor, significantly reversed the observed inhibitory effects of troglitazone. However, GW9662, a specific and irreversible PPARgamma antagonist, did not alter the observed inhibitory effects. Similar results were also found when other TZD drugs, pioglitazone and rosiglitazone, were used. Treatment with various inhibitors revealed that troglitazone-induced inhibitions of tau-Thr231 phosphorylation and p35 expression were not mediated by glycogen synthase kinase 3beta, protein kinase A, and protein phosphatase 2A signaling pathways. Finally, we also found that the same observed inhibitory effects of troglitazone hold true for the use of primary cortical neurons. Taken together, we demonstrated that TZDs repressed tau-Thr231 phosphorylation via the inhibition of CDK5 activity, which was mediated by the proteasomal degradation of p35 and a PPARgamma-independent signaling pathway.

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[213]

**TÍTULO / TITLE:** - Sperm-associated antigen 4, a novel hypoxia-inducible factor 1 target, regulates cytokinesis, and its expression correlates with the prognosis of renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Pathol. 2013 Jun;182(6):2191-203. doi: 10.1016/j.ajpath.2013.02.024. Epub 2013 Apr 17.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ajpath.2013.02.024](#)

**AUTORES / AUTHORS:** - Shoji K; Murayama T; Mimura I; Wada T; Kume H; Goto A; Ohse T; Tanaka T; Inagi R; van der Hoorn FA; Manabe I; Homma Y; Fukayama M; Sakurai T; Hasegawa T; Aburatani H; Kodama T; Nangaku M

**INSTITUCIÓN / INSTITUTION:** - Division of Nephrology and Endocrinology, University of Tokyo, Tokyo, Japan.

**RESUMEN / SUMMARY:** - Hypoxia plays a crucial role in many pathophysiological conditions, including cancer biology, and hypoxia-inducible factor (HIF) regulates transcriptional responses under hypoxia. To elucidate the cellular responses to hypoxia, we performed chromatin immunoprecipitation with deep sequencing in combination with microarray analysis and identified HIF-1 targets. We focused on one of the novel targets, sperm-associated antigen 4 (SPAG4), whose function was unknown. SPAG4, an HIF-1-specific target, is up-regulated in various cultured cells under hypoxia. Examination of SPAG4 expression using a tissue microarray consisting of 190 human renal cell carcinoma (RCC) samples revealed that SPAG4 is an independent prognostic factor of cancer-specific mortality. Live-cell imaging revealed localization of SPAG4 at the intercellular bridge in telophase. We also studied cells in which SPAG4 was knocked down. Hypoxia enhances tetraploidy, which disturbs cell proliferation, and knockdown of SPAG4 increased tetraploid formation and decreased cell proliferation under both normoxic and hypoxic conditions. Studies using deletion mutants of SPAG4 also suggested the involvement of SPAG4 in cytokinesis. Microarray analysis confirmed dysregulation of cytokinesis-related genes by knockdown of SPAG4. In conclusion, SPAG4 is an independent prognostic factor in RCC and plays a crucial role in cytokinesis to defend against hypoxia-induced tetraploid formation. This defensive mechanism may promote survival of cancer cells under hypoxic conditions, thus leading to poor prognosis.

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[214]

**TÍTULO / TITLE:** - Genetic associations with toxicity-related discontinuation of aromatase inhibitor therapy for breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Apr;138(3):807-16. doi: 10.1007/s10549-013-2504-3. Epub 2013 Apr 2.

●●Enlace al texto completo (gratuito o de pago) [1007/s10549-013-2504-](#)

[3](#)

**AUTORES / AUTHORS:** - Henry NL; Skaar TC; Dantzer J; Li L; Kidwell K; Gersch C; Nguyen AT; Rae JM; Desta Z; Oesterreich S; Philips S; Carpenter JS; Storniolo AM; Stearns V; Hayes DF; Flockhart DA

**INSTITUCIÓN / INSTITUTION:** - Breast Oncology Program, University of Michigan Comprehensive Cancer Center, 1500 East Medical Center Drive, Med Inn Bldg C450, Ann Arbor, MI 48109-5843, USA. [norahh@med.umich.edu](mailto:norahh@med.umich.edu)

**RESUMEN / SUMMARY:** - Up to 25 % of patients discontinue adjuvant aromatase inhibitor (AI) therapy due to intolerable symptoms. Predictors of which patients will be unable to tolerate these medications have not been defined. We hypothesized that inherited variants in candidate genes are associated with treatment discontinuation because of AI-associated toxicity. We prospectively evaluated reasons for treatment discontinuation in women with hormone receptor-positive breast cancer initiating adjuvant AI through a multicenter, prospective, randomized clinical trial of exemestane versus letrozole. Using multiple genetic models, we evaluated potential associations between discontinuation of AI therapy because of toxicity and 138 variants in 24 candidate genes, selected a priori, primarily with roles in estrogen metabolism and signaling. To account for multiple comparisons, statistical significance was defined as  $p < 0.00036$ . Of the 467 enrolled patients with available germline DNA, 152 (33 %) discontinued AI therapy because of toxicity. Using a recessive statistical model, an intronic variant in ESR1 (rs9322336) was associated with increased risk of musculoskeletal toxicity-related exemestane discontinuation [HR 5.0 (95 % CI 2.1-11.8),  $p < 0.0002$ ]. An inherited variant potentially affecting estrogen signaling may be associated with exemestane-associated toxicity, which could partially account for intra-patient differences in AI tolerability. Validation of this finding is required.

[215]

**TÍTULO / TITLE:** - Glycogen synthase kinase 3beta inhibition sensitizes human glioblastoma cells to temozolomide by affecting O6-methylguanine DNA methyltransferase promoter methylation via c-Myc signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 28.

●●Enlace al texto completo (gratuito o de pago) [1093/carcin/bqt182](#)

**AUTORES / AUTHORS:** - Pyko IV; Nakada M; Sabit H; Lei T; Furuyama N; Hayashi Y; Kawakami K; Minamoto T; Fedulau AS; Hamada J

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Division of Neuroscience, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, 920-8641, Kanazawa, Ishikawa, Japan.

**RESUMEN / SUMMARY:** - Glycogen synthase kinase 3beta (GSK3beta) is a serine/threonine protein kinase involved in human cancers including

glioblastoma. We have previously demonstrated that GSK3beta inhibition enhances temozolomide effect in glioma cells. In this report, we investigated the molecular mechanisms of sensitization of glioblastoma cells to temozolomide by GSK3beta inhibition, focusing on O6-methylguanine DNA methyltransferase (MGMT) gene silencing. Glioblastoma tissues from patients treated with the GSK3beta-inhibiting drugs were subjected to immunohistochemistry and methylation-specific polymerase chain reaction (MSP) assay. Human glioblastoma cell lines T98G, U138, U251 and U87 were treated with a small-molecule GSK3beta inhibitor, AR-A014418 or GSK3beta-specific siRNA. The combined effect of temozolomide and AR-A014418 on cell proliferation was determined by AlamarBlue assay and an isobologram method. MGMT promoter methylation was estimated by MSP and MethyLight assay. MGMT gene expression was evaluated by real-time quantitative reverse transcriptase-polymerase chain reaction. c-Myc and DNA (cytosine-5)-methyltransferase 3A (DNMT3A) binding to the MGMT promoter was estimated by chromatin immunoprecipitation assay. GSK3beta inhibition decreased phosphorylation of glycogen synthase and reduced MGMT expression, and increased MGMT promoter methylation in clinical tumors. In glioblastoma cell lines, GSK3beta inhibition decreased cell viability, enhanced temozolomide effect, and downregulated MGMT expression with relevant changes in the methylation levels of the MGMT promoter. Here, we showed for the first time that c-Myc binds to the MGMT promoter with consequent recruitment of DNMT3A, regulating the levels of MGMT promoter methylation. The results of this study suggest that GSK3beta inhibition enhances temozolomide effect by silencing MGMT expression via c-Myc-mediated promoter methylation.

[216]

**TÍTULO / TITLE:** - Effects of particle size, food, and capsule shell composition on the oral bioavailability of dabrafenib, a BRAF inhibitor, in patients with BRAF mutation-positive tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pharm Sci. 2013 Apr 22. doi: 10.1002/jps.23519.

●●Enlace al texto completo (gratis o de pago) [1002/jps.23519](#)

**AUTORES / AUTHORS:** - Ouellet D; Grossmann KF; Limentani G; Nebot N; Lan K; Knowles L; Gordon MS; Sharma S; Infante JR; Lorusso PM; Pande G; Krachey EC; Blackman SC; Carson SW

**INSTITUCIÓN / INSTITUTION:** - GlaxoSmithKline, Research Triangle Park, North Carolina. [daniele.x.ouellet@gsk.com](mailto:daniele.x.ouellet@gsk.com).

**RESUMEN / SUMMARY:** - Dabrafenib is a small-molecule inhibitor of BRAF kinase activity that is currently being developed for the treatment of BRAF V600 mutation-positive melanoma. This clinical, open-label, two-cohort (n = 14 per cohort), randomized study was designed to evaluate the effect of drug substance particle size, and food on the plasma pharmacokinetics of a single

oral dose of dabrafenib in patients with BRAF V600 mutation-positive solid tumors. In addition, an exploratory cross-cohort comparison of the relative bioavailability of single-dose dabrafenib administered in gelatin and hydroxypropyl methylcellulose (HPMC) capsules was performed. Higher bioavailability was noted with nonmicronized drug substance (larger particle size), under fasting conditions, and with HPMC capsules. Initial dissolution results at pH 1.2 showed higher dissolution of gelatin relative to HPMC capsules inconsistent with clinical data. Subsequent in vitro dissolution studies were conducted in fasted-state simulated gastric fluid over a 24-h period and showed that HPMC capsules reached a higher percentage of dabrafenib dissolved than gelatin capsules. The presence of HPMC is believed to inhibit precipitation of dabrafenib as the freebase, thereby maintaining a supersaturated solution over an extended period of time. Dabrafenib has been administered in pivotal clinical studies on an empty stomach using micronized drug substance in HPMC capsules. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci.

[217]

**TÍTULO / TITLE:** - Opposing Mcl-1, the GALIG proapoptotic gene is upregulated as neutrophils die and underexpressed in Acute Myeloid Leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Immunol. 2013 May 24;56(1-2):123-128. doi: 10.1016/j.molimm.2013.04.012.

●●Enlace al texto completo (gratis o de pago)

[1016/j.molimm.2013.04.012](#)

**AUTORES / AUTHORS:** - Mollet L; Robinet P; Dubois M; Aurouet A; Normand T; Charpentier S; Sureau A; Grandclement C; Garnache-Ottou F; Deconinck E; Brule F; Rohrlisch PS; Legrand A

**INSTITUCIÓN / INSTITUTION:** - Centre de Biophysique Moleculaire, CNRS UPR 4301, affiliated with the Universite d'Orleans - Pole Universitaire Centre Val de Loire, Rue Charles Sadron, 45071 Orleans Cedex 2, France. Electronic address: [lucile.mollet@cns-orleans.fr](mailto:lucile.mollet@cns-orleans.fr).

**RESUMEN / SUMMARY:** - GALIG gene expression induces apoptosis in cultured cells through a pathway still under investigation. It is highly expressed in leukocytes but weakly detectable in bone marrow, suggesting a role in the myeloid lineage homeostasis. We show here that GALIG-induced cell death is counteracted by the overexpression of MCL-1, a pro-survival member of the Bcl2 family. Moreover, during spontaneous neutrophil apoptosis, a substantial increase in GALIG gene expression is observed: GALIG still opposes MCL-1. Finally, in bone marrow and peripheral blood cells from patients with Acute Myeloid Leukemia type 2, the level of GALIG transcripts is massively down-regulated when compared to their normal counterparts, while MCL-1 is expressed to the same extent. These data suggest that GALIG could be a key

player in the cell death pathway involved in leukocytes homeostasis and myeloid malignancies.

[218]

**TÍTULO / TITLE:** - Efficacy of combined therapy of goserelin and letrozole on very young women with advanced breast cancer as first-line endocrine therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Endocr J. 2013 Mar 1.

**AUTORES / AUTHORS:** - Liu X; Qu H; Cao W; Wang Y; Ma Z; Li F; Wang H

**INSTITUCIÓN / INSTITUTION:** - Department of Galactophore, the Affiliated Hospital of Medical College, Qingdao University, Qingdao, China.

**RESUMEN / SUMMARY:** - Breast cancer in young women younger than 35 years old is rare, aggressive and associated with a poor prognosis. Endocrine therapy is a preferred treatment modality in hormone receptor-positive early stage and advanced breast cancer, combined therapy of goserelin and letrozole presents an option for premenopausal women. We reported the efficacy and safety of therapy of goserelin plus letrozole on very young women with advanced breast cancer as first-line endocrine therapy. Thirty-five patients with first diagnosed as advanced breast cancer, age younger than 35 years, were enrolled in the study. All patients received goserelin 3.6mg by subcutaneous injection every 4 weeks along with letrozole 2.5mg daily by mouth as first-line endocrine therapy. The study endpoints were objective response rate (ORR), clinical benefit (CB), progression-free survival (PFS), overall survival (OS) and toxicity. The median duration of response to the therapy was 21 (range, 10-56) months, and median duration of follow-up was 44 (range, 5-79) months. The ORR was 25.7%, with one complete response (CR, 2.9%) and eight partial response (PR, 22.9%). Twenty-two patients had stable disease at 24 weeks, for a clinical benefit rate of 65.7%. The median PFS was 9.6 (range 5-58) months and median OS was 33 (range 6-72) months. During the therapy and follow-up, no serious toxicities were reported. Combined therapy of goserelin and letrozole appears to be an efficacious and well-tolerated therapy for very young women with advanced breast cancer. Further investigations involving more patients, combination of other therapies and longer follow-up are requisite.

[219]

**TÍTULO / TITLE:** - Efficacy of ponatinib against ABL tyrosine kinase inhibitor-resistant leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 14. pii: S0006-291X(13)00793-6. doi: 10.1016/j.bbrc.2013.05.022.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.022](http://1016/j.bbrc.2013.05.022)

**AUTORES / AUTHORS:** - Okabe S; Tauchi T; Tanaka Y; Ohyashiki K

**INSTITUCIÓN / INSTITUTION:** - First Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan. Electronic address: [okabe@tokyo-med.ac.jp](mailto:okabe@tokyo-med.ac.jp).

**RESUMEN / SUMMARY:** - Because a substantial number of patients with chronic myeloid leukemia acquire resistance to ABL tyrosine kinase inhibitors (TKIs), their management remains a challenge. Ponatinib, also known as AP24534, is an oral multi-targeted TKI. Ponatinib is currently being investigated in a pivotal phase 2 clinical trial. In the present study, we analyzed the molecular and functional consequences of ponatinib against imatinib- or nilotinib-resistant K562 and Ba/F3 cells. The proliferation of imatinib- or nilotinib-resistant K562 cells did not decrease after treatment with imatinib or nilotinib. Src family kinase Lyn was activated. Point mutation Ba/F3 cells (E334V) were also highly resistant to imatinib and nilotinib. Treatment with ponatinib for 72h inhibited the growth of imatinib- and nilotinib-resistant cells. The phosphorylation of BCR-ABL, Lyn, and Crk-L was reduced. This study demonstrates that ponatinib has an anti-leukemia effect by reducing ABL and Lyn kinase activity and this information may be of therapeutic relevance.

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[220]

**TÍTULO / TITLE:** - Pharmacogenetic Angiogenesis Profiling for First-Line Chemotherapy in Patients With Advanced Gastric Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Invest. 2013 May 3.

●●Enlace al texto completo (gratis o de pago)

[3109/07357907.2013.795580](https://doi.org/10.3109/07357907.2013.795580)

**AUTORES / AUTHORS:** - Dan S; Bai L; Li-Jie W; Ting Z; Zhi-Yuan M

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Chinese PLA General Hospital, Postgraduate Medical School, Beijing, China.

**RESUMEN / SUMMARY:** - We retrospectively investigated germline polymorphisms in angiogenesis pathway genes (14 SNPs) and their correlation to clinical outcome (progression free survival and overall survival) in 128 patients with unresectable-advanced gastric carcinoma (AGC) treated with first-line chemotherapy. Our analysis revealed that Endostatin +4349 G>A polymorphism exhibited a worse progression free survival (PFS) and overall survival (OS) compared with the GG genotype. Significant OS difference was also observed in the endothelial nitric oxide synthase (eNOS)-786 T>C polymorphism. Hence, common germline variants in Endostatin and eNOS genes have predictive significance for clinical outcome and survival in AGC patients treated with first-line chemotherapy.

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[221]

**TÍTULO / TITLE:** - The prognostic impact of c-KIT mutation in systemic mastocytosis associated with acute myeloid leukaemia patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 May 14. pii: S0145-2126(13)00142-2.  
doi: 10.1016/j.leukres.2013.04.020.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.04.020](#)

**AUTORES / AUTHORS:** - Won D; Chi HS; Shim H; Jang S; Park CJ; Lee JH

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - We evaluate the haematopathologic features of systemic mastocytosis associated with acute myeloid leukaemia (SM-AML) and the prognostic role of c-KIT mutation. Total 11 patients were enrolled. Cytochemistry using toluidine blue and tryptase was positive, as was immunohistochemistry for CD117 and CD25 on clustered mast cells; however, CD2 was expressed in only nine cases. In 10 cases, RUNX1-RUNX1T1 fusion gene was detected, and one patient presented with a t(5;6)(q22;q23) translocation at diagnosis. The c-KIT mutation D816V was detected in six patients. Patients with c-KIT mutations had higher relapse and death rates than those without; 4/5 (80.0%) and 5/6 (83.3%) vs. 1/5 (20%) and 2/5 (40%), respectively. Overall survival was also significantly shorter in cases with, than those without, c-KIT mutations. To identify rare cases of SM-AML, which have a dismal prognosis, c-KIT mutation study and careful examination for the presence of clustered mast cell infiltration by immunohistochemistry should be performed.

[222]

**TÍTULO / TITLE:** - Ataxia-telangiectasia mutated (ATM) protein expression with microsatellite instability in gastric cancer as prognostic marker.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 May 3. doi: 10.1002/ijc.28245.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28245](#)

**AUTORES / AUTHORS:** - Kim JW; Im SA; Kim MA; Cho HJ; Lee DW; Lee KH; Kim TY; Han SW; Oh DY; Lee HJ; Kim TY; Yang HK; Kim WH; Bang YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - The prognostic significance of ataxia-telangiectasia mutated (ATM) expression in gastric cancer remains unclear. The functional loss of the ATM gene exhibits a biologic correlation with microsatellite instability (MSI). In this study, we investigated the significance of ATM expression with MSI by evaluating gastric cancer patients who had undergone curative resection. ATM expression was classified into low ATM expression (-, +/-, +) and high ATM expression (++, +++) using immunohistochemistry analysis. MSI status was classified as MSI-negative (MSS, MSI-Low) and MSI-positive (MSI-High). Of 321 patients, 205 (63.9%) exhibited low ATM expression and 116

(36.1%) exhibited high ATM expression. Low ATM expression was more frequently identified in patients of older age, more advanced stage, and with MSI-positive tumor ( $p=0.025$ ,  $p=0.001$ , and  $p=0.014$ , respectively). The probability of 5-year disease-free survival (DFS) and overall survival (OS) was lower in low ATM expression group compared to the high ATM expression group (DFS: 62.5%, 76.4%,  $p=0.017$ , OS: 65.9%, 78.5%,  $p=0.027$ , respectively). According to MSI status, a subgroup of MSI-negative and low ATM expression cases exhibited the worst prognosis for DFS and OS; this subgroup also exhibited poorer DFS according to multivariable analysis (HR=1.8, 95% CI, 1.2-2.8,  $p=0.010$ ), although prognostic value of ATM expression alone did not remain in the multivariable analysis. Taken together, these findings indicate that ATM expression with MSI status is an independent factor for gastric cancer prognosis in gastric cancer patients who received curative surgery. © 2013 Wiley Periodicals, Inc.

[223]

**TÍTULO / TITLE:** - Combined p19Arf and interferon-beta gene transfer enhances cell death of B16 melanoma in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Gene Ther. 2013 May;20(5):317-25. doi: 10.1038/cgt.2013.23. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [1038/cgt.2013.23](#)

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**INSTITUCIÓN / INSTITUTION:** - 1] Viral Vector Laboratory, Heart Institute, University of Sao Paulo School of Medicine, Sao Paulo, Brazil [2] Laboratory of Genetics and Molecular Cardiology/LIM13, Heart Institute, University of Sao Paulo School of Medicine, Sao Paulo, Brazil [3] Animal Care Facility, University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

**RESUMEN / SUMMARY:** - Approximately 90% of melanomas retain wild-type p53, a characteristic that may help shape the development of novel treatment strategies. Here, we employed an adenoviral vector where transgene expression is controlled by p53 to deliver the p19 alternate reading frame (Arf) and interferon-beta (IFNbeta) complementary DNAs in the B16 mouse model of melanoma. In vitro, cell death was enhanced by combined gene transfer (63.82±15.30% sub-G0 cells); yet introduction of a single gene resulted in significantly fewer hypoploid cells (37.73±7.3% or 36.96±11.58%, p19Arf or IFNbeta, respectively,  $P<0.05$ ). Annexin V staining and caspase-3 cleavage indicate a cell death mechanism consistent with apoptosis. Using reverse transcriptase quantitative PCR, we show that key transcriptional targets of p53 were upregulated in the presence of p19Arf, although treatment with IFNbeta did not alter expression of the genes studied. In situ gene therapy revealed significant inhibition of subcutaneous tumors by IFNbeta (571±25 mm<sup>3</sup>) or the combination of p19Arf and IFNbeta (489±124 mm<sup>3</sup>) as compared with

the LacZ control (1875+/-33 mm(3), P<0.001), whereas p19Arf yielded an intermediate result (1053+/-169 mm(3), P<0.01 vs control). However, only the combination was associated with increased cell death and prolonged survival (P<0.01). As shown here, the combined transfer of p19Arf and IFNbeta using p53-responsive vectors enhanced cell death both in vitro and in vivo.

[224]

**TÍTULO / TITLE:** - Elevated SGK1 predicts resistance of breast cancer cells to Akt inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem J. 2013 Jun 15;452(3):499-508. doi: 10.1042/BJ20130342.

●●Enlace al texto completo (gratis o de pago) [1042/BJ20130342](#)

**AUTORES / AUTHORS:** - Sommer EM; Dry H; Cross D; Guichard S; Davies BR; Alessi DR

**INSTITUCIÓN / INSTITUTION:** - \*MRC Protein Phosphorylation and Ubiquitylation Unit, College of Life Sciences, University of Dundee, Dundee DD1 5EH, U.K.

**RESUMEN / SUMMARY:** - The majority of human cancers harbour mutations promoting activation of the Akt protein kinase, and Akt inhibitors are being evaluated in clinical trials. An important question concerns the understanding of the innate mechanisms that confer resistance of tumour cells to Akt inhibitors. SGK (serum- and glucocorticoid-regulated kinase) is closely related to Akt and controlled by identical upstream regulators {PI3K (phosphoinositide 3-kinase), PDK1 (phosphoinositide-dependent kinase 1) and mTORC2 [mTOR (mammalian target of rapamycin) complex 2]}. Mutations that trigger activation of Akt would also stimulate SGK. Moreover, Akt and SGK possess analogous substrate specificities and are likely to phosphorylate overlapping substrates to promote proliferation. To investigate whether cancers possessing high SGK activity could possess innate resistance to Akt-specific inhibitors (that do not target SGK), we analysed SGK levels and sensitivity of a panel of breast cancer cells towards two distinct Akt inhibitors currently in clinical trials (AZD5363 and MK-2206). This revealed a number of Akt-inhibitor-resistant lines displaying markedly elevated SGK1 that also exhibited significant phosphorylation of the SGK1 substrate NDRG1 [N-Myc (neuroblastoma-derived Myc) downstream-regulated gene 1]. In contrast, most Akt-inhibitor-sensitive cell lines displayed low/undetectable levels of SGK1. Intriguingly, despite low SGK1 levels, several Akt-inhibitor-sensitive cells showed marked NDRG1 phosphorylation that was, unlike in the resistant cells, suppressed by Akt inhibitors. SGK1 knockdown markedly reduced proliferation of Akt-inhibitor-resistant, but not -sensitive, cells. Furthermore, treatment of Akt-inhibitor-resistant cells with an mTOR inhibitor suppressed proliferation and led to inhibition of SGK1. The results of the present study suggest that monitoring SGK1 levels as well as responses of NDRG1 phosphorylation to Akt inhibitor administration could have a use in

predicting the sensitivity of tumours to compounds that target Akt. Our findings highlight the therapeutic potential that SGK inhibitors or dual Akt/SGK inhibitors might have for treatment of cancers displaying elevated SGK activity.

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[225]

**TÍTULO / TITLE:** - Synergistic relationship between dipeptidyl peptidase IV and neutral endopeptidase expression and the combined prognostic significance in osteosarcoma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):608. doi: 10.1007/s12032-013-0608-6. Epub 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0608-](#)

[6](#)

**AUTORES / AUTHORS:** - Zhang H; Lin H; Mo X; Chen G; Lin L

**INSTITUCIÓN / INSTITUTION:** - Orthopedics Department, Zhongshan City People's Hospital, Zhongshan, 528403, China.

**RESUMEN / SUMMARY:** - Neutral endopeptidase (NEP/CD10) and dipeptidyl peptidase IV (DPP IV/CD26) are both ubiquitous glycopeptidases which play important roles in tumor pathogenesis and development. The aim of this study was to investigate the expression patterns and the prognostic significance of CD10 and CD26 in osteosarcoma patients. CD10 and CD26 expression in 116 pairs of primary osteosarcoma and corresponding noncancerous bone tissue samples from the same specimens were detected by immunohistochemistry. The Spearman's correlation was calculated between the expression levels of CD10 and CD26 in osteosarcoma tissues. The associations of CD10 and CD26 expression with the clinicopathologic features and with the prognosis of osteosarcoma were subsequently assessed. Both CD10 expression and CD26 expression in osteosarcoma tissues were significantly higher than those in corresponding noncancerous bone tissue samples (both  $P < 0.001$ ). Overexpression of CD10 and CD26 were respectively observed in 68.10 % (79/116) and 70.69 % (82/116) of osteosarcoma tissues. A significant correlation was found between CD10 expression and CD26 expression in osteosarcoma tissues ( $r = 0.83$ ,  $P < 0.001$ ). In addition, combined overexpression of CD10 and CD26 was observed in 52.59 % (61/116) of osteosarcoma tissues. CD10-high/CD26-high expression was significantly correlated with advanced clinical stage ( $P = 0.001$ ), positive metastatic status ( $P = 0.001$ ), shorter overall ( $P < 0.001$ ) and disease-free ( $P < 0.001$ ) survival in patients with osteosarcomas. Furthermore, multivariate survival analysis showed that clinical stage, metastatic status, CD10 expression, CD26 expression and combined expression of CD10/CD26 were all independent prognostic factors for predicting both overall and disease-free survival of osteosarcoma patients. Interestingly, combined expression of CD10/CD26 had a better prognostic value than other features. This retrospective study offer the

convincing evidence for the first time that the overexpression of CD10 or CD26 may be an important feature of human osteosarcomas, and the combined expression of CD10/CD26 may be an efficient prognostic indicator for this disease.

[226]

**TÍTULO / TITLE:** - TLR8 stimulation enhances cetuximab-mediated natural killer cell lysis of head and neck cancer cells and dendritic cell cross-priming of EGFR-specific CD8 T cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Immunol Immunother. 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s00262-013-1437-](http://1007/s00262-013-1437-3)

[3](#)

**AUTORES / AUTHORS:** - Stephenson RM; Lim CM; Matthews M; Dietsch G; Hershberg R; Ferris RL

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Cetuximab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody that prolongs survival in the treatment for head and neck cancer (HNC), but only in 10-20 % of patients. An immunological mechanism of action such as natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) has been suggested. We investigated the effects of activating toll-like receptor (TLR)-8 to enhance activity of cetuximab-stimulated, FcγR-bearing cells. OBJECTIVE: To determine the capability of TLR8-stimulation to enhance the activation and function of NK cells and dendritic cells (DC) in the presence of cetuximab-coated HNC cells. METHODS: Peripheral blood mononuclear cells (PBMC), NK, DC, and CD8+ T cells were isolated and analyzed using <sup>51</sup>Cr release ADCC, flow cytometry analysis, cytokine ELISA, and EGFR853-861 tetramer staining. RESULTS: TLR8 stimulation of unfractionated PBMC led to enhanced cetuximab-mediated ADCC in healthy donors ( $p < 0.01$ ) and HNC patients ( $p < 0.001$ ), which was dependent on NK cells. Secretion of Th1 cytokines TNFα ( $p < 0.0001$ ), IFNγ ( $p < 0.0001$ ), and IL-12p40 ( $p < 0.005$ ) was increased. TLR8 stimulation of PBMC augmented cetuximab-enhanced NK cell degranulation ( $p < 0.001$ ). TLR8-stimulated NK cells enhanced DC maturation markers CD80, CD83, and CD86 in co-culture with cetuximab-treated HNC cells. TLR8 stimulation of NK-DC co-cultures significantly increased DC priming of EGFR-specific CD8+ T cells in the presence of cetuximab. DISCUSSION: VTX-2337 and cetuximab combination therapy can activate innate and adaptive anti-cancer immune responses. Further investigation in human trials will be important for determining the clinical benefit of this combination and for determining biomarkers of response.

[227]

**TÍTULO / TITLE:** - Notch inhibition restores TRAIL-mediated apoptosis via AP1-dependent upregulation of DR4 and DR5 TRAIL receptors in MDA-MB-231 breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):121-30. doi: 10.3892/ijo.2013.1945. Epub 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1945](#)

**AUTORES / AUTHORS:** - Portanova P; Notaro A; Pellerito O; Sabella S; Giuliano M; Calvaruso G

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Medicina traslazionale, Università del Piemonte Orientale, Novara, Italy.

**RESUMEN / SUMMARY:** - Notch is a family of transmembrane receptors whose activation through proteolytic cleavage by gamma-secretase targets genes which participate in cell development, differentiation and tumorigenesis. Notch signaling is constitutively activated in various cancers, including breast cancer and its upregulation is usually related with poor clinical outcomes. Therefore, targeting Notch signaling with gamma-secretase inhibitors (GSIs) is considered a promising strategy for cancer treatment. We report that the gamma-secretase inhibitor-I (GSI-I) sensitizes human breast cancer cells to apoptosis mediated by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The antiproliferative GSI-I/TRAIL synergism was stronger in ER-negative MDA-MB-231 breast cancer cells compared with ER-positive MCF-7 cells. In MDA-MB-231 cells, GSI-I treatment induced upregulation of DR4 and DR5 TRAIL receptors. This effect seemed to be related to the activation of the transcription factor AP1 that was a consequence of Notch inhibition, as demonstrated by Notch-1 silencing experiments. Combined treatment induced loss of the mitochondrial transmembrane potential and activation of caspases. GSI-I alone and/or GSI-I/TRAIL combination also induced a significant decrease in the levels of some survival factors (survivin, c-IAP-2, Bcl-xL, BimEL and pAKT) and upregulation of pro-apoptotic factors BimL, BimS and Noxa, enhancing the cytotoxic potential of the two drugs. Taken together, these results indicate for the first time that GSI-I/TRAIL combination could represent a novel and potentially effective tool for breast cancer treatment.

[228]

**TÍTULO / TITLE:** - Melatonin reverses tunicamycin-induced endoplasmic reticulum stress in human hepatocellular carcinoma cells and improves cytotoxic response to doxorubicin by increasing CHOP and decreasing Survivin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pineal Res. 2013 Apr 24. doi: 10.1111/jpi.12061.

●●Enlace al texto completo (gratis o de pago) [1111/jpi.12061](http://1111/jpi.12061)

**AUTORES / AUTHORS:** - Fan L; Sun G; Ma T; Zhong F; Lei Y; Li X; Wei W

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China.

**RESUMEN / SUMMARY:** - Chemoresistance in hepatocellular carcinoma (HCC) is associated with multiple cellular responses to environmental stresses, such as nutrient deprivation and hypoxia. Nevertheless, whether ER stress resulting from nutrient deprivation and tumor hypoxia contributes to drug resistance remains unclear. Melatonin increased the efficacy of chemotherapeutic drugs in hepatocellular carcinoma in our previous studies. However, the effects of melatonin on endoplasmic reticulum (ER) stress-induced resistance to chemotherapeutic agents in HCC have not been tested. The effect of the endoplasmic reticulum (ER) stress response during resistance of human hepatocellular carcinoma cells against doxorubicin was investigated in this study. Pretreatment of HepG2 and SMMC-7721 cells (two human hepatocellular carcinoma cell lines) with tunicamycin, an ER stress inducer, drastically decreased the rate of apoptosis generated by doxorubicin. Interestingly, co-pretreatment with tunicamycin and melatonin significantly increased apoptosis induced by doxorubicin. Simultaneously, the expression of phosphorylated AKT (p-AKT) was elevated in HepG2 and SMMC-7721 cells given tunicamycin but reduced in the presence of melatonin. Furthermore, consistent with inhibition of AKT activation by using the PI3K inhibitor LY294002, melatonin elevated the levels of CHOP (C/EBP-homologous protein) and reduced the levels of Survivin (a member of the inhibitor of apoptosis protein family) suggesting that inhibition of the PI3K/AKT pathway by melatonin-reversed ER stress-induced resistance to doxorubicin in human hepatocellular carcinoma cells. These results demonstrate that melatonin attenuates ER stress-induced resistance to doxorubicin in human hepatocellular carcinoma cells by down-regulating the PI3K/AKT pathway, increasing the levels of CHOP and decreasing the levels of Survivin.

[229]

**TÍTULO / TITLE:** - Histone Deacetylase Inhibitors Interact with MDA-7/IL-24 to Kill Primary Human Glioblastoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Pharmacol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1124/mol.113.086553](http://1124/mol.113.086553)

**AUTORES / AUTHORS:** - Hamed HA; Yacoub A; Park MA; Archer K; Das SK; Sarkar D; Grant S; Fisher PB; Dent P

**INSTITUCIÓN / INSTITUTION:** - VCU.

**RESUMEN / SUMMARY:** - We presently demonstrate that histone deacetylase inhibitors (HDACIs) enhance toxicity of melanoma differentiation associated gene-7/interleukin 24 (mda-7/IL-24) in invasive primary human GBM cells.

Additionally, a method is described to augment efficacy of adenoviral delivery of mda-7/IL-24 in these cells. HDACIs synergized with MDA-7/IL-24 killing GBM cells. Enhanced lethality correlated with increased autophagy that was dependent on expression of ceramide synthase 6. HDACIs interacted with MDA-7/IL-24 prolonging generation of ROS and Ca<sup>2+</sup>. Quenching of ROS and Ca<sup>2+</sup> blocked HDACI and MDA-7/IL-24 killing. In vivo MDA-7/IL-24 prolonged survival of animals carrying orthotopic tumors and HDACIs enhanced survival further. A serotype 5/3 adenovirus more effectively delivers mda-7/IL-24 to GBM tumors than a serotype 5 virus. Hence, we constructed a serotype 5/3 adenovirus that conditionally replicates in tumor cells expressing MDA-7/IL-24, in which the adenoviral E1A gene was driven by the cancer-specific promoter progression elevated gene-3 (Ad.5/3-PEG-E1A-mda-7; also called Ad.5/3-CTV). Ad.5/3-CTV increased survival of mice carrying GBM tumors to a significantly greater extent than did a non-replicative virus Ad.5/3-mda-7. Ad.5/3-CTV exhibited no toxicity in the brains of Syrian hamsters. Collectively our data demonstrates that HDACIs enhance MDA-7/IL-24 lethality and adenoviral delivery of mda-7/IL-24 combined with tumor specific viral replication is an effective pre-clinical GBM therapeutic.

[230]

**TÍTULO / TITLE:** - Anticancer Activity of Phyllanthus emblica Linn. (Indian Gooseberry): Inhibition of Transcription Factor AP-1 and HPV Gene Expression in Cervical Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65 Suppl 1:88-97. doi: 10.1080/01635581.2013.785008.

●●Enlace al texto completo (gratis o de pago)

[1080/01635581.2013.785008](#)

**AUTORES / AUTHORS:** - Mahata S; Pandey A; Shukla S; Tyagi A; Husain SA; Das BC; Bharti AC

**INSTITUCIÓN / INSTITUTION:** - a Division of Molecular Oncology , Institute of Cytology and Preventive Oncology (Indian Council of Medical Research) , Uttar Pradesh , India.

**RESUMEN / SUMMARY:** - Plant products of Phyllanthus emblica Linn. are traditionally consumed for its immense nutritive and medicinal values. However, the molecular mechanism(s) by which it exerts its effects is less understood. In this study, we investigated mechanism of action of P. emblica fruit extract (PE) by studying its effect on activator protein-1 (AP-1) activity and human papillomavirus (HPV) transcription that are essential for tumorigenicity of cervical cancer cells. PE resulted in a dose- and time-dependent inhibition of DNA binding activity of constitutively active AP-1 in both HPV16-positive (SiHa) and HPV18-positive (HeLa) cervical cancer cells. PE-induced AP-1 inhibition was found mediated through downregulation of constituent AP-1 proteins, c-

Jun, JunB, JunD, and c-Fos; however, the kinetics of their inhibition varied in both the cell types. Inhibition of AP-1 by PE was accompanied by suppression of viral transcription that resulted in growth inhibition of cervical cancer cells. Growth inhibitory activity of PE was primarily manifested through induction of apoptotic cell death. These results suggest that *P. emblica* exhibits its anticancer activities through inhibition of AP-1 and targets transcription of viral oncogenes responsible for development and progression of cervical cancer thus indicating its possible utility for treatment of HPV-induced cervical cancers.

[231]

**TÍTULO / TITLE:** - A Common and Functional Gene Variant in the Vascular Endothelial Growth Factor A Predicts Clinical Outcome in Early-Stage Breast Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 Apr 26. doi: 10.1002/mc.22028.

●●Enlace al texto completo (gratis o de pago) [1002/mc.22028](#)

**AUTORES / AUTHORS:** - Absenger G; Szkandera J; Stotz M; Pichler M; Winder T; Langsenlehner T; Langsenlehner U; Samonigg H; Renner W; Gerger A

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Oncology, Department of Internal Medicine, Medical University Graz, Graz, Austria.

**RESUMEN / SUMMARY:** - Angiogenesis and cell cycle control play critical roles in breast cancer susceptibility and clinical outcome and are mainly controlled by vascular endothelial growth factor (VEGF) and cyclin-dependent kinases, respectively. Functional germline polymorphisms in these genes alter the function, thereby causing inter-individual differences in breast cancer risk and clinical outcome. In this study, we investigated the influence of the functional polymorphisms VEGF-A rs3025039 C > T and CCND1 rs9344 G > A on risk and clinical outcome in early-stage breast cancer. DNA of 539 female patients with histologically confirmed early-stage breast cancer and 804 control subjects was genotyped for these polymorphisms. Genotypes were tested for associations with breast cancer risk and clinical outcome. There was no significant association between the polymorphisms and breast cancer risk. However, the minor allele of VEGF-A rs3025039 C > T was significantly associated with decreased recurrence-free survival (HR 1.845; 95% confidence interval [CI] 1.035-3.290; P = 0.038) and remained significant in multivariate analysis (HR 1.880; 95% CI 1.020-3.465; P = 0.043). Patients carrying at least one A-allele in CCND1 rs9344 G > A showed a trend towards decreased recurrence-free survival in univariate analysis (HR 2.379; 95% CI 0.841-6.728; P = 0.068). This study provides evidence that the functional VEGF-A rs3025039 C > T polymorphism influences recurrence-free survival in early-stage breast cancer. © 2013 Wiley Periodicals, Inc.

[232]

**TÍTULO / TITLE:** - Distinct patterns of novel gene mutations in poor-prognostic stereotyped subsets of chronic lymphocytic leukemia: the case of SF3B1 and subset #2.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leukemia. 2013 May 3. doi: 10.1038/leu.2013.98.

●●Enlace al texto completo (gratis o de pago) [1038/leu.2013.98](#)

**AUTORES / AUTHORS:** - Strefford JC; Sutton LA; Baliakas P; Agathangelidis A; Malcikova J; Plevova K; Scarfo L; Davis Z; Stalika E; Cortese D; Cahill N; Pedersen LB; di Celle PF; Tzenou T; Geisler C; Panagiotidis P; Langerak AW; Chiorazzi N; Pospisilova S; Oscier D; Davi F; Belessi C; Mansouri L; Ghia P; Stamatopoulos K; Rosenquist R

**INSTITUCIÓN / INSTITUTION:** - Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK.

**RESUMEN / SUMMARY:** - Recent studies have revealed recurrent mutations of the NOTCH1, SF3B1 and BIRC3 genes in chronic lymphocytic leukemia (CLL), especially among aggressive, chemorefractory cases. Nevertheless, it is currently unknown whether their presence may differ in subsets of patients carrying stereotyped B-cell receptors and also exhibiting distinct prognoses. Here, we analyzed the mutation status of NOTCH1, SF3B1 and BIRC3 in three subsets with particularly poor prognosis, that is, subset #1, #2 and #8, aiming to explore links between genetic aberrations and immune signaling. A remarkably higher frequency of SF3B1 mutations was revealed in subset #2 (44%) versus subset #1 and #8 (4.6% and 0%, respectively;  $P < 0.001$ ). In contrast, the frequency of NOTCH1 mutations in subset #2 was only 8%, lower than the frequency observed in either subset #1 or #8 (19% and 14%, respectively;  $P = 0.04$  for subset #1 versus #2). No associations were found for BIRC3 mutations that overall were rare. The apparent non-random association of certain mutations with stereotyped CLL subsets alludes to subset-biased acquisition of genomic aberrations, perhaps consistent with particular antigen/antibody interactions. These novel findings assist in unraveling specific mechanisms underlying clinical aggressiveness in poor-prognostic stereotyped subsets, with far-reaching implications for understanding their clonal evolution and implementing biologically oriented therapy. Leukemia advance online publication, 3 May 2013; doi:10.1038/leu.2013.98.

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[233]

**TÍTULO / TITLE:** - Tumour necrosis factor alpha blockers are more effective than methotrexate in the inhibition of radiographic joint damage progression among patients with psoriatic arthritis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Rheum Dis. 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1136/annrheumdis-2012-202959](#)

**AUTORES / AUTHORS:** - Eder L; Thavaneswaran A; Chandran V; Gladman DD

**INSTITUCIÓN / INSTITUTION:** - University of Toronto Psoriatic Arthritis Clinic, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, Toronto, Ontario, Canada.

**RESUMEN / SUMMARY:** - AIM: To determine whether tumour necrosis factor alpha (TNFalpha) blockers are more effective than methotrexate in inhibiting the progression of radiographic joint damage in patients with psoriatic arthritis (PsA). METHODS: A cohort analysis of patients followed prospectively in a large PsA clinic was conducted. Patients who received a TNFalpha blocker were compared to those treated with methotrexate. Patients who had records of at least 12 months of treatment with either medication for active peripheral PsA and had radiographic bone erosions were analysed. Radiographs of the hands and feet were performed at baseline, 1-2 years (time 1) and 3-4 years (time 2). Radiographic joint damage was scored according to the modified Steinbrocker score. The outcome of interest was the occurrence of radiographic progression. Multivariate logistic regression analysis using generalised estimating equations for repeated measures was used to compare progression in radiographic joint damage between the two treatment groups. RESULTS: 65 patients treated with TNFalpha blockers and 70 patients treated with methotrexate were analysed. The proportion of patients who demonstrated progression of radiographic damage score at time 1 and time 2 was higher in the methotrexate group compared to the TNFalpha blockers group (at time 1: 80% vs 58.9% p=0.005; at time 2: 88% vs 61% p=0.005). In the multivariate regression analysis methotrexate treatment was associated with an increase in radiographic damage compared to TNFalpha blockers (p=0.001). CONCLUSIONS: In a clinic setting, patients with erosive PsA receiving TNFalpha blockers had a better radiographic outcome compared to those treated with methotrexate.

[234]

**TÍTULO / TITLE:** - Polymorphisms in ERCC1 C8092A predict progression-free survival in metastatic/recurrent nasopharyngeal carcinoma treated with cisplatin-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2196-8](#)

**AUTORES / AUTHORS:** - Chen C; Wang F; Wang Z; Li C; Luo H; Liang Y; An X; Shao J; Li Y

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Sun Yat-Sen University Cancer Center, 651<sup>st</sup> Dongfeng Road East, Guangzhou, 510060, Guangdong, China.

**RESUMEN / SUMMARY:** - OBJECTIVES: We evaluated whether DNA repair gene polymorphisms had an effect on clinical outcomes in metastatic/recurrent nasopharyngeal carcinoma (NPC) patients treated with cisplatin-based chemotherapy. MATERIALS AND METHODS: Clinical data of 101 patients with metastatic/recurrent NPC between 2004 and 2011 were reviewed. Five potentially functional polymorphisms (ERCC1 Asn118Asn, ERCC1 C8092A, XPD Lys751Gln, XRCC1 Arg399Gln and XRCC1 Arg280His) were genotyped using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. RESULTS: The ERCC1 C8092A polymorphism was an independent predictor of PFS in Chinese NPC patients treated with cisplatin-based chemotherapy. Compared to the patients carrying the C/C genotype, the patients with the C/A or A/A genotype had an increased risk of disease progression on cisplatin-based chemotherapy (7.9 vs. 9.3 months; HR 1.61; 95 % CI 1.08-2.61; p = 0.047). However, no association between the other polymorphisms, response rate, disease progression and survival was detected in metastatic/recurrent NPC patients. CONCLUSION: The ERCC1 C8092A polymorphism might be a useful predictive marker in metastatic/recurrent NPC patients treated with cisplatin-based chemotherapy. However, a large-scale prospective study is warranted to validate our findings.

[235]

**TÍTULO / TITLE:** - An antiapoptotic Bcl-2 family protein index predicts the response of leukaemic cells to the pan-Bcl-2 inhibitor S1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Mar 14;108(9):1870-8. doi: 10.1038/bjc.2013.152. Epub 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.152](#)

**AUTORES / AUTHORS:** - Zhang Z; Liu Y; Song T; Xue Z; Shen X; Liang F; Zhao Y; Li Z; Sheng H

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Fine Chemicals, School of Chemistry, Dalian University of Technology, Dalian 116024, China.

**RESUMEN / SUMMARY:** - Background: Bcl-2-like members have been found to be inherently overexpressed in many types of haematologic malignancies. The small-molecule S1 is a BH3 mimetic and a triple inhibitor of Bcl-2, Mcl-1 and Bcl-XL. Methods: The lethal dose 50 (LD50) values of S1 in five leukaemic cell lines and 41 newly diagnosed leukaemia samples were tested. The levels of Bcl-2 family members and phosphorylated Bcl-2 were semiquantitatively measured by western blotting. The interactions between Bcl-2 family members were tested by co-immunoprecipitation. The correlation between the LD50 and expression levels of Bcl-2 family members, alone or in combination, was analysed. Results: S1 exhibited variable sensitivity with LD50 values ranging >2 logs in both established and primary leukaemic cells. The ratio of pBcl-2/(Bcl-2+Mcl-1) could predict the S1 response. Furthermore, we demonstrated that

pBcl-2 antagonised S1 by sequestering the Bak and Bim proteins that were released from Mcl-1, and pBcl-2/Bak, pBcl-2/Bax and pBcl-2/Bim complexes cannot be disrupted by S1. Conclusion: A predictive index was obtained for the novel BH3 mimetic S1. The shift of proapoptotic proteins from being complexed with Mcl-1 to being complexed with pBcl-2 was revealed for the first time, which is the mechanism underlying the index value described herein.

[236]

**TÍTULO / TITLE:** - The combination of the antiestrogen endoxifen with all-trans-retinoic acid has anti-proliferative and anti-migration effects on melanoma cells without inducing significant toxicity in non-neoplastic cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 May 24. pii: S0014-2999(13)00344-0. doi: 10.1016/j.ejphar.2013.04.038.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ejphar.2013.04.038](#)

**AUTORES / AUTHORS:** - Ribeiro MP; Silva FS; Paixao J; Santos AE; Custodio JB  
**INSTITUCIÓN / INSTITUTION:** - Center for Neuroscience and Cell Biology, University of Coimbra, 3000-354 Coimbra, Portugal; Laboratory of Biochemistry, Faculty of Pharmacy, University of Coimbra, 3000-548 Coimbra, Portugal.

**RESUMEN / SUMMARY:** - Melanoma incidence is dramatically increasing and the available treatments beyond partial efficacy have severe side effects. Retinoids are promising anticancer agents, but its clinical use has been limited by their toxicity, although a combination with other agents can possibly generate a therapeutic action at lower dosage. Thus, we investigated the effects of all-trans-retinoic acid combined with the antiestrogen endoxifen on melanoma cell proliferation and the effects were compared with its pro-drug tamoxifen. Moreover, we evaluated the effects of these combinations on non-neoplastic cells and assessed mitochondrial bioenergetic functions, to predict their potential toxicity. Individually, all-trans-retinoic acid and the antiestrogens endoxifen and tamoxifen decreased melanoma cell biomass, cell viability and DNA synthesis, without increased cell death, suggesting that the compounds inhibited cell proliferation. Noteworthy, endoxifen decreased cell proliferation more efficiently than tamoxifen. The combination of endoxifen with all-trans-retinoic acid enhanced the antiproliferative effects of the compounds individually more potently than tamoxifen, which did not enhance the effects induced by all-trans-retinoic acid alone, and blocked cell cycle progression in G1. Moreover, the combination of all-trans-retinoic acid with endoxifen significantly decreased melanoma cells migration, whereas the combination with tamoxifen did not present significant effects. At the concentrations used the compounds did not induce cytotoxicity in non-neoplastic cells and liver mitochondrial bioenergetic function was not affected. Altogether, our results show for the first time that a combined treatment of all-trans-retinoic acid with

endoxifen may provide an anti-proliferative and anti-migration effect upon melanoma cells without major toxicity, offering a powerful therapeutic strategy for malignant melanoma.

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[237]

**TÍTULO / TITLE:** - Diminishing prognostic role of preexisting diabetes mellitus for patients with diffuse large B-cell lymphoma in the rituximab era.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1789-](http://1007/s00277-013-1789-)

[y](#)

**AUTORES / AUTHORS:** - Lu HJ; Huang YC; Liu CY; Hung MH; Hu MH; Wu CY; Hong YC; Hsiao LT; Gau JP; Liu JH; Hsu HC; Chiou TJ; Tzeng CH; Yu YB

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - Rituximab reforms the treatment of diffuse large B-cell lymphoma (DLBCL) and the prognostic significance of baseline patient features should be reevaluated. Few population-based studies have investigated the association of diabetes mellitus (DM) and outcomes of lymphoma; however, the results remain inconclusive. From January 1, 2000 to December 31, 2009, a total of 468 consecutive newly diagnosed DLBCL patients receiving first-line chemotherapy with cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) or rituximab plus CHOP (R-CHOP) were enrolled. Pre-existing DM was defined according to medical history, use of antidiabetic medications, or any record of an abnormal hemoglobin A1c test. Progression-free survival (PFS) and overall survival (OS) were estimated and compared using the Kaplan-Meier method with a log-rank test. CHOP was administered in 194 patients, and 274 patients received R-CHOP. DM was identified in 16.2 % (76/468) of patients. Diabetic patients were older and more performance restricted, compared to the non-DM patients in both the CHOP and R-CHOP groups. In the CHOP group, 5-year PFS and OS were inferior in DM patients (PFS, 32.4 vs. 50.0 % (P = 0.039); OS, 38.2 vs. 62.5 % (P = 0.002)). However, outcomes were similar for both DM and non-DM patients in the context of R-CHOP treatment (PFS, 69.0 vs. 57.3 % (P = 0.179); OS, 76.2 vs. 69.8 % (P = 0.586)). The response rate of chemotherapy in DM patients was also improved to a level similar to non-DM patients with rituximab use. In conclusion, the prognostic significance of preexisting DM in DLBCL patients is changing in the rituximab era. The potentially additional benefit of rituximab in DM patients merits further investigation.

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[238]

**TÍTULO / TITLE:** - Overexpression of long noncoding RNA PCAT-1 is a novel biomarker of poor prognosis in patients with colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):588. doi: 10.1007/s12032-013-0588-6. Epub 2013 May 3.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0588-](#)

[6](#)

**AUTORES / AUTHORS:** - Ge X; Chen Y; Liao X; Liu D; Li F; Ruan H; Jia W

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, Guangzhou, China.

**RESUMEN / SUMMARY:** - Long noncoding RNAs (lncRNA) are emerging as key molecules in human cancer. Prostate cancer-associated ncRNA transcripts 1 (PCAT-1), a lncRNA, has been recently revealed involving in human prostate cancer progression. However, whether PCAT-1 could serve as novel biomarker to predict prognosis in colorectal cancer (CRC) or not is unknown. We therefore carried out the present study to explore the correlation between PCAT-1 expression and the progression of CRC. In this study, the expression of PCAT-1 in 108 cases of CRC tissues and matched 81 adjacent normal tissues were determined by quantitative real-time PCR. Furthermore, the copy number variation of PCAT-1 was also measured in 17 tumor tissues and matched normal tissues. Our results showed that PCAT-1 expression in CRC tissues was significantly upregulated compared with the matched normal tissues ( $p < 0.001$ ) and the overexpression of PCAT-1 (upregulated by more than 50 %) was found in 64 % (62/81) of CRC. Moreover, PCAT-1 gene copy number variation explains only a few percent of observed overexpression. In addition, there was a significant association between PCAT-1 expression and distant metastasis ( $p = 0.04$ ), but not other clinical characteristics. More important, CRC patients with PCAT-1 higher expression have shown significantly poorer overall survival than those with lower PCAT-1 expression ( $p < 0.001$ ). Also, multivariable Cox regression analysis identified PCAT-1 overexpression as an independent prognostic factor for CRC ( $p = 0.007$ , HR = 3.12 95 %CI = 1.355-7.185). In conclusion, our results suggest that high expression of PCAT-1 is involved in CRC progression and could be a novel biomarker of poor prognosis in patient with colorectal cancer.

[239]

**TÍTULO / TITLE:** - Imatinib disrupts lymphoma angiogenesis by targeting vascular pericytes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1182/blood-2013-03-490763](#)

**AUTORES / AUTHORS:** - Ruan J; Luo M; Wang C; Fan L; Yang SN; Cardenas M; Geng H; Leonard JP; Melnick A; Cerchietti L; Hajjar KA

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology/Oncology, Department of Medicine, Weill Cornell Medical College, New York, NY, United States;

**RESUMEN / SUMMARY:** - Pericytes and vascular smooth muscle cells (VSMC), which are recruited to developing blood vessels by platelet-derived growth factor BB, support endothelial cell survival and vascular stability. Here, we report that imatinib, a tyrosine kinase inhibitor of PDGFRbeta, impaired growth of lymphoma in both human xenograft and murine allograft models. Lymphoma cells themselves neither expressed PDGFRbeta nor were growth-inhibited by imatinib. Tumor growth inhibition was associated with decreased microvascular density and increased vascular leakage. In vivo, imatinib induced apoptosis of tumor-associated PDGFRbeta+ pericytes and loss of perivascular integrity. In vitro, imatinib inhibited PDGFRbeta+ VSMC proliferation and PDGF-BB signaling, while siRNA knockdown of PDGFRbeta in pericytes protected them against imatinib-mediated growth inhibition. FACS analysis of tumor tissue revealed depletion of pericytes, endothelial cells, and their progenitors following imatinib treatment. Compared to imatinib, treatment with an anti-PDGFRbeta monoclonal antibody partially inhibited lymphoma growth. Lastly, microarray analysis (GEO database accession number: GSE30752) of PDGFRbeta+ VSMC following imatinib treatment showed down-regulation of genes implicated in vascular cell proliferation, survival, and assembly, including those representing multiple pathways downstream of PDGFRbeta. Taken together, these data indicate that PDGFRbeta+ pericytes may represent a novel, non-endothelial, anti-angiogenic target for lymphoma therapy.

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[240]

**TÍTULO / TITLE:** - Transglutaminase 2 inhibition found to induce p53 mediated apoptosis in renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - FASEB J. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1096/fj.12-224220](#)

**AUTORES / AUTHORS:** - Ku BM; Kim DS; Kim KH; Yoo BC; Kim SH; Gong YD; Kim SY

**INSTITUCIÓN / INSTITUTION:** - \*Cancer Cell and Molecular Biology Branch, Division of Cancer Biology, and daggerColorectal Cancer Branch, Division of Translational and Clinical Research I, Research Institute, National Cancer Center, Goyang, Korea; and.

**RESUMEN / SUMMARY:** - Renal cell carcinoma (RCC), the predominant form of kidney cancer, is characterized by high resistance to radiation and chemotherapy. This study shows that expression of protein cross-linking enzyme transglutaminase 2 (TGase 2) is markedly increased in 7 renal cell carcinoma (RCC) cell lines in comparison to HEK293 and other cancer cell

lines, such as NCI 60. However, the key role of TGase 2 in RCC was not clear. The down-regulation of TGase 2 was found to stabilize p53 expression, thereby inducing a 3- to 10-fold increase in apoptosis for 786-O, A498, CAKI-1, and ACHN cell lines by DAPI staining. MEF cells from TGase 2<sup>-/-</sup> mice showed stabilized p53 under apoptotic stress to compare to MEFs from wild-type mice. TGase 2 directly cross links the DNA binding domain of p53, leading to p53 depletion via autophagy in RCC. TGase 2 and p53 expression showed an inverse relationship in RCC cells. This finding implies that induced expression of TGase 2 promotes tumor cell survival through p53 depletion in RCC.-Ku, B.M., Kim, D.-S. Kim, K.-H., Yoo, B.C., Kim, S.-H., Gong, Y.-D., Kim, S.-Y. Transglutaminase 2 inhibition found to induce p53 mediated apoptosis in renal cell carcinoma.

[241]

**TÍTULO / TITLE:** - What is the relevance of Ikaros gene deletions as prognostic marker in pediatric Philadelphia negative B-cell precursor acute lymphoblastic leukemia?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago)

[3324/haematol.2012.075432](#)

**AUTORES / AUTHORS:** - Palmi C; Valsecchi MG; Longinotti G; Silvestri D; Carrino V; Conter V; Basso G; Biondi A; Te Kronnie G; Cazzaniga G

**INSTITUCIÓN / INSTITUTION:** - Clinica Pediatrica, Università' di Milano-Bicocca, Monza, Italy;

**RESUMEN / SUMMARY:** - We herewith focused the analysis of Ikaros gene deletions in a homogeneous cohort of 410 pediatric non-Down syndrome and Philadelphia chromosome-negative, B-cell precursor Acute Lymphoblastic Leukemia patients enrolled in Italy into the AIEOP-BFM ALL2000 study. We confirm their reported poor prognostic value, although the associated Event-free survival was relatively high (approximately 70%). The difference in the Cumulative incidence of relapse between patients positive or not for IKZF1 deletions was not marked (24.2% (5.9) vs 13.1% (1.8) overall and 23.9% (6.6) vs 16.5% (2.5) in the Intermediate risk subgroup). In line with this, IKZF1 deletions were not an independent prognostic factor of the hazard of relapse. Moreover, most IKZF1 deleted cases stratified in the high risk group relapsed, thus suggesting that their identification would then require an alternative treatment. In conclusion, the need and benefit of introducing IKZF1 deletions as an additional stratification marker for Ph negative BCP-ALL patients remains questionable.

[242]

**TÍTULO / TITLE:** - RNH1 regulation of reactive oxygen species contributes to histone deacetylase inhibitor resistance in gastric cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncogene. 2013 Apr 15. doi: 10.1038/onc.2013.104.

●●Enlace al texto completo (gratis o de pago) [1038/onc.2013.104](#)

**AUTORES / AUTHORS:** - Zhu Y; Das K; Wu J; Lee MH; Tan P

**INSTITUCIÓN / INSTITUTION:** - [1] Cancer and Stem Cell and Biology, Duke-NUS Graduate Medical School, Singapore [2] Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

**RESUMEN / SUMMARY:** - Histone deacetylase inhibitors (HDACis) are a promising class of anticancer epigenetic drugs, however, molecular factors influencing the responses of individual tumors to HDACi therapies remain obscure. Here, we sought to identify genes associated with HDACi resistance in gastric cancer. Treating a panel of 17 gastric cancer cell lines with multiple HDACi compounds (trichostatin A, SAHA and MS275), we identified two distinct classes of lines exhibiting either HDACi sensitivity or resistance. Genomic comparisons between the sensitive and resistant classes using two independent microarray platforms identified RNH1, encoding a ribonuclease inhibitor, as a gene highly expressed in HDACi-resistant lines. Using genetic knockdown and overexpression assays, we show that RNH1 is both necessary and sufficient to induce HDACi resistance, and that RNH1 is likely to mediate this resistance through the dampening of HDACi-induced reactive oxygen species (ROS) in cancer cells. The discovery of RNH1 as a regulator of HDACi resistance in gastric cancer highlights a functional role for ROS induction in the cellular effects of this important drug class. Oncogene advance online publication, 15 April 2013; doi:10.1038/onc.2013.104.

[243]

**TÍTULO / TITLE:** - Histology as a potential clinical predictor of outcome in advanced non-small-cell lung cancer treated with vinorelbine and mitomycin combination chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung. 2013 Jun;191(3):271-80. doi: 10.1007/s00408-013-9458-4. Epub 2013 Apr 7.

●●Enlace al texto completo (gratis o de pago) [1007/s00408-013-9458-](#)

[4](#)

**AUTORES / AUTHORS:** - Wibmer T; Berghmans T; Kropf-Sanchen C; Lafitte JJ; Rudiger S; Paesmans M; Blanta I; Scherpereel A; Stoiber KM; Rottbauer W; Sculier JP; Schumann C

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine II, University Hospital of Ulm, Albert-Einstein-Allee 23, 89081, Ulm, Germany.

**RESUMEN / SUMMARY:** - BACKGROUND: The importance of clinical predictors in the treatment of non-small-cell lung cancer (NSCLC) has increased during the

last decade. This retrospective study analyzed the combined patient-level data from two phase II trials that investigated the efficacy and safety of combination chemotherapy with vinorelbine and mitomycin in patients with locally advanced or metastatic NSCLC. The aim of this analysis was to determine if patients' baseline and disease characteristics, including histology, gender, smoking history, and expression of TTF-1, might be potential predictors of outcome. METHODS: Response rates, unadjusted survival times, and Cox covariate-adjusted hazard ratios (HRs) were calculated. Results were reported separately for each subgroup in each individual trial and in the pooled data set. RESULTS: A total of 175 patients were included in this analysis. Adjusted HRs for both overall survival (OS) and progression free survival (PFS) favored the nonadenocarcinoma histology subgroup, achieving a statistical significance for OS in the pooled data (n = 175; HR 0.68; 95 % CI 0.49-0.94; p = 0.019). TTF-1-negative immunohistochemistry was associated with a significantly higher response rate (25 vs. 0 %; p = 0.04) and with a nonsignificant advantage in OS (n = 33; HR 1.23; 95 % CI 0.56-2.73; p = 0.608). Gender and smoking history were not strongly related to outcome. CONCLUSIONS: The results of this analysis indicate that patients with nonadenocarcinoma histology might get superior benefit from combination chemotherapy with vinorelbine and mitomycin. These results should be confirmed in a prospective study.

[244]

**TÍTULO / TITLE:** - Phase I, dose-finding study of AZD8931, an inhibitor of EGFR (erbB1), HER2 (erbB2) and HER3 (erbB3) signaling, in patients with advanced solid tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Invest New Drugs. 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1007/s10637-013-9963-](#)

[6](#)

**AUTORES / AUTHORS:** - Tjulandin S; Moiseyenko V; Semiglazov V; Manikhas G; Learoyd M; Saunders A; Stuart M; Keilholz U

**INSTITUCIÓN / INSTITUTION:** - N. N. Blokhin Russian Cancer Research Centre of RAMS, Kashirskoe Shosse 24, 115478, Moscow, Russia, [stjulandin@gmail.com](mailto:stjulandin@gmail.com).

**RESUMEN / SUMMARY:** - Aim AZD8931 is an oral equipotent inhibitor of EGFR (erbB1), HER2 (erbB2) and HER3 (erbB3) signaling. This Phase I, open-label study evaluated the safety, tolerability, and pharmacokinetics of multiple ascending doses of AZD8931 in patients with advanced solid tumors ( NCT00637039 ). Methods Patients received AZD8931 as a single oral dose followed by 4 days of observation, then twice-daily dosing for 21 consecutive days. Using a standard 3 + 3 design, AZD8931 doses were escalated from 40 mg bid until the maximum tolerated dose (MTD) was established. Results Twenty-eight patients received AZD8931 (n = 5, 40 mg bid; n = 8, 80 mg bid; n

= 6, 160 mg bid; n = 6, 240 mg bid; n = 3, 300 mg bid). Ovary (n = 8) and breast (n = 5) were the most common primary tumor types. The most frequent adverse events were treatment-emergent cutaneous (n = 27) and diarrhea (n = 21). Dose-limiting toxicities (DLTs) were identified in one patient in the 240 mg bid cohort (Grade 3 rash) and two patients in the 300 mg bid cohort (Grade 3 and 4 diarrhea). The pharmacokinetic profile of AZD8931 supported twice-daily dosing. AZD8931 was rapidly absorbed (median t<sub>max</sub> 1-3 h), was well distributed and had moderate to high clearance with an elimination half-life of approximately 11 h. Exposure appeared to increase approximately proportionally with dose up to 160 mg. Of 21 patients evaluable for response at day 21, 12 had stable disease and nine had disease progression. Conclusion The MTD of AZD8931 determined from the 21-day DLT period was 240 mg bid, although more long-term data are needed to confirm a dose of AZD8931 suitable for chronic treatment.

[245]

**TÍTULO / TITLE:** - Re: A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: the cancer and osteoporosis research with alendronate and leuprolide (CORAL) study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Urol. 2013 May;189(5):1714. doi: 10.1016/j.juro.2013.01.075. Epub 2013 Jan 30.

●●Enlace al texto completo (gratis o de pago) [1016/j.juro.2013.01.075](http://1016/j.juro.2013.01.075)

**AUTORES / AUTHORS:** - Taneja SS

[246]

**TÍTULO / TITLE:** - Flow cytometric analysis of lymphocyte apoptosis in newly diagnosed patients with lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 21.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.797089](http://3109/10428194.2013.797089)

**AUTORES / AUTHORS:** - Gunduz E; Uskudar Teke H; Akay OM; Gulbas Z

**INSTITUCIÓN / INSTITUTION:** - Eskisehir Osmangazi University School of Medicine Department of Hematology , Eskisehir , Turkey.

[247]

**TÍTULO / TITLE:** - Synergistic effects of metformin treatment in combination with gefitinib, a selective EGFR tyrosine kinase inhibitor, in LKB1 wild-type NSCLC cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-2777](#)

**AUTORES / AUTHORS:** - Morgillo F; Sasso FC; Della Corte CM; Vitagliano D; D'aiuto E; Troiani T; Martinelli E; De Vita F; Orditura M; De Palma R; Ciardiello F

**INSTITUCIÓN / INSTITUTION:** - Dipartimento medico chirurgico di Internistica clinica e sperimentale, Second University of Naples.

**RESUMEN / SUMMARY:** - **PURPOSE:** Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been found to be effective against lung cancer, but clinical resistance to these agents has developed as their usage has increased. Metformin is a widely used antidiabetic drug and also displays significant growth inhibitory and pro apoptotic effects in several cancer models, alone or in combination with chemotherapeutic drugs. Experimental design: The effects of gefitinib, a selective EGFR-TKI, and metformin on a panel of NSCLC cell lines were assessed by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT), bromide assay, flow cytometry, anchorage independent growth, co-immunoprecipitation, and Western blot analysis. **RESULTS:** The combination of metformin with gefitinib induced a strong antiproliferative and proapoptotic effect in NSCLC cell lines which harbored wild type LKB1 gene. Treatment with metformin as single agent, however, induced an activation and phosphorylation of MAPK through an increased C-RAF:B-RAF heterodimerization. The inhibition of EGFR phosphorylation and of downstream signaling by adding gefitinib to metformin treatment abrogated this phenomenon and induced a strong apoptotic effect in vitro and in vivo. **CONCLUSIONS:** Metformin and gefitinib are synergistic in LKB1 wild type NSCLC cells. However, further studies are required to investigate better the effect of metformin action on the RAS/RAF/MAPK pathway and the best context in which to use metformin in combination with molecular targeted agents.

[248]

**TÍTULO / TITLE:** - UGT1A1\*6/\*28 polymorphisms could predict irinotecan-induced severe neutropenia not diarrhea in Chinese colorectal cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):604. doi: 10.1007/s12032-013-0604-x. Epub 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0604-x](#)

**AUTORES / AUTHORS:** - Gao J; Zhou J; Li Y; Lu M; Jia R; Shen L

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of

Education), Peking University, Cancer Hospital & Institute, No. 52, Fucheng Road, Haidian District, Beijing, 100142, China.

**RESUMEN / SUMMARY:** - The aim of this study was to investigate the associations between UDP-glucuronosyltransferase (UGT) 1A1 polymorphisms and irinotecan-induced toxicities in Chinese advanced colorectal cancer patients. The genotypes of UGT1A1\*6 and UGT1A1\*28 were analyzed by PCR amplification and Sanger sequencing in 276 advanced colorectal cancer patients receiving irinotecan-containing chemotherapy. The influences of UGT1A1\*6/\*28 polymorphisms on severe diarrhea and neutropenia were analyzed. The overall incidence of UGT1A1\*6 and UGT1A1\*28 variants was 35.5 % (GA: 28.6 %; AA: 6.9 %) and 21.0 % (TA6/TA7: 19.9 %; TA7/TA7: 1.1 %) in our cohort, respectively. A total of 16 patients (5.8 %, 16/276) had severe diarrhea and 56 patients (20.3 %, 56/276) had severe neutropenia. Neither UGT1A1\*6 nor UGT1A1\*28 variants were associated with severe diarrhea; however, either UGT1A1\*6 (P = 0.001) or UGT1A1\*28 (P = 0.029) variants were significantly associated with severe neutropenia. No differences were found between severe toxicities and clinical response in this study. Compared to western countries, Chinese patients had a distinct frequency of UGT1A1\*6 or UGT1A1\*28 genotypes. Both UGT1A1\*6 and UGT1A1\*28 variants were closely associated with irinotecan-induced severe neutropenia, but not diarrhea.

[249]

**TÍTULO / TITLE:** - Silencing of indoleamine 2,3-dioxygenase enhances dendritic cell immunogenicity and antitumour immunity in cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):280-8. doi: 10.3892/ijo.2013.1922. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1922](#)

**AUTORES / AUTHORS:** - Sioud M; Saeboe-Larssen S; Hetland TE; Kaern J; Mobergslien A; Kvalheim G

**INSTITUCIÓN / INSTITUTION:** - Department of Immunology, Oslo University Radium Hospital, Montebello, N-0310 Oslo, Norway.

**RESUMEN / SUMMARY:** - Dendritic cells (DCs) are being explored as a therapeutic vaccine for cancers. However, their immunogenic potential is limited by the presence of immunosuppressive factors. Among these factors is the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO). In this study, we have investigated the safety, immunogenicity and clinical response of IDO-silenced DC vaccine in four patients with gynecological cancers. DCs were transfected with IDO small interfering RNA and mRNA encoding human telomerase reverse transcriptase (hTERT) or survivin, two universal tumour antigens. Silencing of IDO in DCs did not affect the expression of the co-stimulatory molecules CD80 and CD86, but enhanced the expression of the CCR7 and CD40 molecules. IDO-silenced DCs showed superior potency to

activate allogeneic T cells compared to their IDO-positive counterparts. The immunisation with this novel DC cancer vaccine was well tolerated and all patients developed delayed-type hypersensitivity skin reaction and specific T-cell response against hTERT and survivin tumour antigens. Perhaps most importantly, the immune response seen in the patients was related to objective clinical response. Thus, IDO silencing can enhance the immunogenic function of DCs in vitro and in vivo. Overall, the data provide proof-of-principle that immunisation with IDO-silenced DC vaccine is safe and effective in inducing antitumour immunity.

[250]

**TÍTULO / TITLE:** - The positive correlation between DJ-1 and beta-catenin expression shows prognostic value for patients with glioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neuropathology. 2013 May 28. doi: 10.1111/neup.12041.

●●Enlace al texto completo (gratis o de pago) [1111/neup.12041](#)

**AUTORES / AUTHORS:** - Wang C; Fang M; Zhang M; Li W; Guan H; Sun Y; Xie S; Zhong X

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Medical College, Jinan University.

**RESUMEN / SUMMARY:** - The relationship between DJ-1 and beta-catenin, and its impact on the prognosis for glioma patients has not been fully understood. This study determined the effect of DJ-1 on beta-catenin and the prognostic significance of this interaction in glioma patients. We collected tumor specimens from 88 glioma patients and determined the expression of DJ-1, beta-catenin and PTEN by using immunohistochemical staining. The involvement of DJ-1 and beta-catenin in glioma cell lines was evaluated by immunohistochemistry and Western blotting. High DJ-1 expression (37.5%) and high beta-catenin expression (34.1%) in glioma specimens were significantly associated with high grade and poor prognosis in glioma patients. However, only high levels of DJ-1 ( $P = 0.014$ ) was a strong independent prognostic factor, correlated with a reduced overall survival time. In vitro DJ-1 expression was positively correlated with the expression levels of beta-catenin and p-Akt, and negatively correlated with PTEN expression in U87, U251 MG, SWO-38 and SHG44 human glioma cell lines. After the knockdown of DJ-1, Akt, p-Akt or beta-catenin expression levels were not affected in the PTEN-null cell lines (U87 and U251 MG). However, in the SWO-38 cell line, which has wild-type PTEN protein, the level of PTEN increased while Akt/p-Akt and beta-catenin levels were reduced. Furthermore, beta-catenin staining weakened in SWO-38 cells after DJ-1 levels decreased according to immunocytochemical analysis. In conclusion, DJ-1 and beta-catenin may contribute to the development and recurrence of glioma and are valuable prognostic factors for glioma patients. DJ-1 may regulate beta-catenin expression via PTEN and p-Akt.

[251]

**TÍTULO / TITLE:** - Perfusion CT allows prediction of therapy response in non-small cell lung cancer treated with conventional and anti-angiogenic chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur Radiol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1007/s00330-013-2821-](http://1007/s00330-013-2821-2)

[2](#)

**AUTORES / AUTHORS:** - Tacelli N; Santangelo T; Scherpereel A; Duhamel A; Deken V; Klotz E; Cortot A; Lafitte JJ; Wallyn F; Remy J; Remy-Jardin M

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Imaging, Hospital Calmette (EA 2694), University of Lille Nord de France, 59000, Lille, France.

**RESUMEN / SUMMARY:** - **OBJECTIVES:** To determine whether CT can depict early perfusion changes in lung cancer treated by anti-angiogenic drugs, allowing prediction of response. **METHODS:** Patients with non-small cell lung cancer, treated by conventional chemotherapy with (Group 1; n = 17) or without (Group 2; n = 23) anti-vascular endothelial growth factor (anti-VEGF) drug (bevacizumab) underwent CT perfusion before (TIME 0) and after 1 (TIME 1), 3 (TIME 2) and 6 (TIME 3) cycles of chemotherapy. The CT parameters evaluated included: (1) total tumour vascular volume (TVV) and total tumour extravascular flow (TEF); (2) RECIST (Response Evaluation Criteria in Solid Tumours) measurements. Tumour response was also assessed on the basis of the clinicians' overall evaluation. **RESULTS:** In Group 1, significant reduction in perfusion was identified between baseline and: (1) TIME 1 (TVV, P = 0.0395; TEF, P = 0.015); (2) TIME 2 (TVV, P = 0.0043; TEF, P < 0.0001); (3) TIME 3 (TVV, P = 0.0034; TEF, P = 0.0005) without any significant change in Group 2. In Group 1: (1) the reduction in TVV at TIME 1 was significantly higher in responders versus non-responders at TIME 2 according to RECIST (P = 0.0128) and overall clinicians' evaluation (P = 0.0079); (2) all responders at TIME 2 had a concurrent decrease in TVV and TEF at TIME 1. **CONCLUSION:** Perfusion CT demonstrates early changes in lung cancer vascularity under anti-angiogenic chemotherapy that may help predict therapeutic response. **KEY POINTS :** \* Perfusion CT has the potential of providing in vivo information about tumour vasculature. \* CT depicts early and specific perfusion changes in NSCLC under anti-angiogenic drugs. \* Specific therapeutic effects of anti-angiogenic drugs can be detected before tumour shrinkage. \* Early perfusion changes can help predict therapeutic response to anti-angiogenic treatment. \* Perfusion CT could be a non-invasive tool to monitor anti-angiogenic treatment.

[252]

**TÍTULO / TITLE:** - Haptoglobin proved a prognostic biomarker in peripheral blood of patients with personalized Peptide vaccinations for advanced castration-resistant prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biosci Biotechnol Biochem. 2013 Apr 23;77(4):766-70. Epub 2013 Apr 7.

**AUTORES / AUTHORS:** - Pang X; Tashiro K; Eguchi R; Komatsu N; Sasada T; Itoh K; Kuhara S

**INSTITUCIÓN / INSTITUTION:** - Graduate School of Systems Life Sciences, Kyushu University.

**RESUMEN / SUMMARY:** - Haptoglobin (Hp) is a well-known acute-phase protein that possibly has influence on tumors through the immune response. This study was conducted to evaluate the correlation between Hp expression and the effect of treatment by cancer peptide vaccines in advanced castration-resistant prostate cancer (CRPC) patients. Hp expression was measured by RT-PCR using peripheral blood mononuclear cells (PBMCs) collected from advanced CRPC patients, who were divided into two groups: long-term survivors and short-term survivors. Before cancer peptide vaccination (pre-vaccination), Hp expression was almost same in the two groups, but after cancer peptide vaccination (post-vaccination), Hp expression was higher in short-term survivors, suggesting that Hp expression in the PBMCs increased in short-term survivors after treatment by cancer peptide vaccines. Our results suggest that Hp expression level in the PBMCs can serve as a prognostic biomarker in treatment by cancer peptide vaccine in advanced CRPC patients.

[253]

**TÍTULO / TITLE:** - Activation of AMP-activated protein kinase (AMPK) mediates plumbagin-induced apoptosis and growth inhibition in cultured human colon cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Signal. 2013 May 25. pii: S0898-6568(13)00157-5. doi: 10.1016/j.cellsig.2013.05.026.

●●Enlace al texto completo (gratis o de pago)

[1016/j.cellsig.2013.05.026](http://dx.doi.org/10.1016/j.cellsig.2013.05.026)

**AUTORES / AUTHORS:** - Chen MB; Zhang Y; Wei MX; Shen W; Wu XY; Yao C; Lu PH

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Kunshan First People's Hospital Affiliated to Jiangsu University, 91 Qianjin Road, Kunshan 215300, Jiangsu Province, China.

**RESUMEN / SUMMARY:** - Here we report that activation of AMP-activated protein kinase (AMPK) mediates plumbagin-induced apoptosis and growth inhibition in both primary cultured human colon cancer cells and cell lines. Knocking-down of AMPK $\alpha$  by the target shRNA significantly inhibits plumbagin-induced

cytotoxicity in cultured colon cancer cells, while forced activation of AMPK by introducing a constitutively active AMPK (CA-AMPK), or by the AMPK activator, inhibits HT-29 colon cancer cell growth. Our Western-blots and immunoprecipitation (IP) results demonstrate that plumbagin induces AMPK/Apoptosis signal regulating kinase 1 (ASK1)/TNF receptor-associated factor 2 (TRAF2) association to activate pro-apoptotic c-Jun N-terminal kinases (JNK)-p53 signal axis. Further, after plumbagin treatment, activated AMPK directly phosphorylates Raptor to inhibit mTOR complex 1 (mTORC1) activation and Bcl-2 expression in colon cancer cells. Finally, we found that exogenously-added short-chain ceramide (C6) enhances plumbagin-induced AMPK activation and facilitates cell apoptosis and growth inhibition. Our results suggest that AMPK might be the key mediator of plumbagin's anti-tumor activity.

[254]

**TÍTULO / TITLE:** - Molecular mechanisms of Lycoris aurea agglutinin-induced apoptosis and G2 /M cell cycle arrest in human lung adenocarcinoma A549 cells, both in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Prolif. 2013 Jun;46(3):272-82. doi: 10.1111/cpr.12034.

●●Enlace al texto completo (gratis o de pago) [1111/cpr.12034](#)

**AUTORES / AUTHORS:** - Li CY; Wang Y; Wang HL; Shi Z; An N; Liu YX; Liu Y; Zhang J; Bao JK; Deng SP

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences & Key Laboratory of Bio-resources, Ministry of Education, Sichuan University, Chengdu, China.

**RESUMEN / SUMMARY:** - OBJECTIVES: Lycoris is aurea agglutinin (LAA) has attracted rising attention due to its remarkable bioactivities. Here, we aimed at investigating its anti-tumor activities. MATERIAL AND METHODS: In vitro methods including MTT, cellular morphology observation, FCM and immunoblotting were performed. In vivo methods like detection of tumor volume, body weight and survival ratio, as well as TUNEL staining were performed. RESULTS AND CONCLUSION: LAA triggers G2 /M phase cell cycle arrest via up-regulating p21 expression as well as down-regulating cdk-1 cyclinA signaling pathway, and induces apoptotic cell death through inhibiting PI3K-Akt survival pathway in human lung adenocarcinoma A549 cells. While LAA has no significant cytotoxic effect toward normal human embryonic lung fibroblast HELF cells, and moreover, LAA could amplify the antineoplastic effects of cisplatin toward A549 cells. Lastly LAA also bears anti-cancer and apoptosis-inducing effects in vivo, and it could decrease the volume and weight of subcutaneous tumor mass obviously as well as expand lifespan of mice. These findings may provide a new perspective for elucidating the complicated molecular mechanisms of LAA-induced cancer cell growth-inhibition and death,

providing a new opportunity of LAA as a potential candidate anti-neoplastic drug for future cancer therapeutics.

[255]

**TÍTULO / TITLE:** - RNA interference-mediated silencing of NANOG leads to reduced proliferation and self-renewal, cell cycle arrest and apoptosis in T-cell acute lymphoblastic leukemia cells via the p53 signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 May 14. pii: S0145-2126(13)00143-4. doi: 10.1016/j.leukres.2013.04.021.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.04.021](#)

**AUTORES / AUTHORS:** - Cao J; Li L; Chen C; Lv C; Meng F; Zeng L; Li Z; Wu Q; Zhao K; Pan B; Cheng H; Chen W; Xu K

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Nanjing Medical University, Nanjing, China; Department of Hematology, the Affiliated Hospital of Xuzhou Medical College, Xuzhou, China.

**RESUMEN / SUMMARY:** - NANOG is critical for maintaining the self-renewal and proliferative properties of embryonic stem cells. Here we found that cultured T-cell acute lymphoblastic leukemia (T-ALL) cells, as well as human primary T-ALL cells, express a functional variant of NANOG. NANOG mRNA is derived predominantly from a retrogene locus termed NANOGP8. Furthermore, we showed that RNA interference-mediated NANOG knockdown inhibited cell proliferation, reduced self-renewal, promoted apoptosis and arrested the cell cycle through a p53-mediated pathway in leukemic cells. These findings demonstrate the oncogenic potential of this pluripotent gene in human T-ALL cells.

[256]

**TÍTULO / TITLE:** - Antitumor activity of pimasertib, a selective MEK 1/2 inhibitor, in combination with PI3K/mTOR inhibitors or with multi-targeted kinase inhibitors in pimasertib-resistant human lung and colorectal cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Apr 30:0. doi: 10.1002/ijc.28236.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28236](#)

**AUTORES / AUTHORS:** - Martinelli E; Troiani T; D'Aiuto E; Morgillo F; Vitagliano D; Capasso A; Costantino S; Ciuffreda LP; Merolla F; Vecchione L; De Vriendt V; Tejpar S; Nappi A; Sforza V; Martini G; Berrino L; De Palma R; Ciardiello F

**INSTITUCIÓN / INSTITUTION:** - Oncologia Medica, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale "F. Magrassi e A. Lanzara", Seconda Universita degli Studi di Napoli, Via S. Pansini 5, 80131, Napoli, Italia.

**RESUMEN / SUMMARY:** - The RAS/RAF/MEK/MAPK and the PTEN/PI3K/AKT/mTOR pathways are key regulators of proliferation and survival in human cancer cells. Selective inhibitors of different transducer molecules in these pathways have been developed as molecular targeted anti-cancer therapies. The in vitro and in vivo anti-tumor activity of pimasertib, a selective MEK ½ inhibitor, alone or in combination with a PI3K inhibitor (PI3Ki), a mTOR inhibitor (everolimus), or with multi-targeted kinase inhibitors (sorafenib and regorafenib), that block also BRAF and CRAF, were tested in a panel of eight human lung and colon cancer cell lines. Following pimasertib treatment, cancer cell lines were classified as pimasertib-sensitive (IC50 for cell growth inhibition of 0.001 microM) or pimasertib-resistant. Evaluation of basal gene expression profiles by microarrays identified several genes that were up-regulated in pimasertib-resistant cancer cells and that were involved in both RAS/RAF/MEK/MAPK and PTEN/PI3K/AKT/mTOR pathways. Therefore, a series of combination experiments with pimasertib and either PI3Ki, everolimus, sorafenib or regorafenib were conducted, demonstrating a synergistic effect in cell growth inhibition and induction of apoptosis with sustained blockade in MAPK- and AKT-dependent signaling pathways in pimasertib-resistant human colon carcinoma (HCT15) and lung adenocarcinoma (H1975) cells. Finally, in nude mice bearing established HCT15 and H1975 subcutaneous tumor xenografts, the combined treatment with pimasertib and BEZ235 (a dual PI3K/mTOR inhibitor) or with sorafenib caused significant tumor growth delays and increase in mice survival as compared to single agent treatment. These results suggest that dual blockade of MAPK and PI3K pathways could overcome intrinsic resistance to MEK inhibition.

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[257]

**TÍTULO / TITLE:** - Human Equilibrative Nucleoside Transporter 1 (hENT1) Predicts the Asian Patient Response to Gemcitabine-Based Chemotherapy in Pancreatic Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatogastroenterology. 2013 Mar-Apr;60(122):258-62. doi: 10.5754/hge12687.

●●Enlace al texto completo (gratis o de pago) [5754/hge12687](#)

**RESUMEN / SUMMARY:** - Background/Aims: Individualized chemotherapy is important in the treatment of pancreatic cancer. Therefore, markers for predicting a patient response to treatment must be identified. We studied the relationship between human equilibrative nucleoside transporter 1 (hENT1) expression in tumor cells and the Asian patient response to gemcitabine-based chemotherapy. The aim of the study was to identify markers for individualized chemotherapy in Asian patients with pancreatic cancer. Methodology: Specimens from 44 Asian patients diagnosed with pancreatic adenocarcinoma were analyzed by immunohistochemistry for hENT1 expression in tumor cells.

The correlations between hENT1 expression and various clinicopathological factors, including survival status, were studied. Results: The overall survival (OS) and disease-free survival (DFS) in the hENT1 high-expression group were significantly longer than those of the hENT1 low or no-expression group: OS 21.75 months (95%CI=18.45-25.04 months) vs. 12.48 months (95%CI=10.12-14.85 months); DFS 15.44 months (95%CI=11.26-19.62 months) vs. 8.24 months (95%CI=8.69-9.78 months), respectively. Conclusions: Our studies suggest that hENT1 expression is related to the patient response to gemcitabine-based chemotherapy in Asian patients with pancreatic cancer. Therefore, hENT1 may be a valuable prognostic marker for individualized chemotherapy in pancreatic cancer.

[258]

**TÍTULO / TITLE:** - Proteomic analysis reveals that pardaxin triggers apoptotic signaling pathways in human cervical carcinoma HeLa cells: cross talk among the UPR, c-Jun and ROS.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 28.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bqt130](#)

**AUTORES / AUTHORS:** - Huang TC; Chen JY

**INSTITUCIÓN / INSTITUTION:** - Marine Research Station, Institute of Cellular and Organismic Biology, Academia Sinica, 23-10 Dahuen Road, Jiaushi, Ilan 262, Taiwan.

**RESUMEN / SUMMARY:** - Pardaxin, an antimicrobial peptide secreted by the Red Sea flatfish *Pardachirus marmoratus*, inhibits proliferation and induces apoptosis of human cancer cell lines. However, the underlying molecular mechanisms are only partially understood at present. In this study, we used proteomic approaches and network reconstruction to clarify the mechanism of pardaxin-induced apoptosis in human cervical carcinoma HeLa cells. We identified that pardaxin-regulated proteins predominantly function in the unfolded protein response, oxidative stress and cytoskeletal distribution. Molecular examination of signal transduction and cellular localization demonstrated that the activator protein-1 transcription factor was activated, which eventually caused apoptosis via both caspase- and apoptosis-inducing factor-dependent pathways. Scavenging of reactive oxygen species (ROS) alleviated c-Jun activation, and small interfering RNA knockdown of c-Jun abrogated pardaxin-induced caspase activation and cell death, thereby implicating ROS and c-Jun in pardaxin-induced apoptosis signaling. In summary, this study provides the first protein-interacting network maps and novel insights into the biological responses and potential toxicity of pardaxin.

[259]

**TÍTULO / TITLE:** - Pathologic complete response to neoadjuvant chemotherapy with trastuzumab predicts for improved survival in women with HER2-overexpressing breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt131](#)

**AUTORES / AUTHORS:** - Kim MM; Allen P; Gonzalez-Angulo AM; Woodward WA; Meric-Bernstam F; Buzdar AU; Hunt KK; Kuerer HM; Litton JK; Hortobagyi GN; Buchholz TA; Mittendorf EA

**INSTITUCIÓN / INSTITUTION:** - Departments of Radiation Oncology.

**RESUMEN / SUMMARY:** - BACKGROUND: We sought to determine the prognostic value of pathologic response to neoadjuvant chemotherapy with concurrent trastuzumab. PATIENTS AND METHODS: Two hundred and twenty-nine women with HER2/neu (HER2)-overexpressing breast cancer were treated with neoadjuvant chemotherapy plus trastuzumab between 2001 and 2008. Patients were grouped based on pathologic complete response (pCR, n = 114) or less than pCR (<pCR, n = 115); as well as by pathologic stage. Locoregional recurrence-free (LRFS), distant metastasis-free (DMFS), recurrence-free (RFS), and overall survival (OS) rates were compared. RESULTS: The median follow-up was 63 (range 53-77) months. There was no difference in clinical stage between patients with pCR or <pCR. Compared with patients achieving <pCR, those with the pCR had higher 5-year rates of LRFS (100% versus 95%, P = 0.011), DMFS (96% versus 80%, P < 0.001), RFS (96% versus 79%, P < 0.001), and OS (95% versus 84%, P = 0.006). Improvements in RFS and OS were seen with decreasing post-treatment stage. Failure to achieve a pCR was the strongest independent predictor of recurrence (hazard ratio [HR] = 4.09, 95% confidence interval [CI]: 1.67-10.04, P = 0.002) and death (HR = 4.15, 95% CI: 1.39-12.38, P = 0.011). CONCLUSIONS: pCR and lower pathologic stage after neoadjuvant chemotherapy with trastuzumab are the strongest predictors of recurrence and survival and are surrogates of the long-term outcome in patients with HER2-overexpressing disease.

[260]

**TÍTULO / TITLE:** - Apoptosis induction in human glioblastoma multiforme T98G cells upon temozolomide and quercetin treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0785-](#)

[0](#)

**AUTORES / AUTHORS:** - Jakubowicz-Gil J; Langner E; Badziul D; Wertel I; Rzeski W

**INSTITUCIÓN / INSTITUTION:** - Department of Comparative Anatomy and Anthropology, Maria Curie-Skłodowska University, Akademicka 19, 20-033, Lublin, Poland, [jigil@poczta.umcs.lublin.pl](mailto:jigil@poczta.umcs.lublin.pl).

**RESUMEN / SUMMARY:** - Glioblastoma multiforme is the most aggressive primary brain tumour. At the cellular and molecular levels, several mechanisms responsible for apoptosis or autophagy induction are blocked. Identification of molecular targets stimulating cells to initiate programmed cell death should be performed for therapeutic purposes. A promising solution is the combination of temozolomide and quercetin. The aim of our study was to evaluate the effect of both drugs, applied alone and in combinations, on apoptosis and autophagy induction in human glioblastoma multiforme T98G cells. Our results clearly indicate that quercetin and temozolomide induce apoptosis very significantly, having no effect on autophagy induction. At the molecular level, it was correlated with caspase 3 and 9 activation, cytochrome c release from the mitochondrion and a decrease in the mitochondrial membrane potential. Both drugs are also potent Hsp27 and Hsp72 inhibitors. This suggests that the apoptotic signal goes through an internal pathway. Increased expression of caspase 12 and the presence of several granules in the cytoplasm after temozolomide treatment with or without quercetin preceding appearance of apoptosis may suggest that apoptosis is initiated by ER stress. Additionally, it was accompanied by changes in the nuclear morphology from circular to 'croissant like'.

[261]

**TÍTULO / TITLE:** - The association of taxane resistance genes with the clinical course of ovarian carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genomics. 2013 Mar 28. pii: S0888-7543(13)00058-X. doi: 10.1016/j.ygeno.2013.03.005.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygeno.2013.03.005](http://1016/j.ygeno.2013.03.005)

**AUTORES / AUTHORS:** - Ehrlichova M; Mohelnikova-Duchonova B; Hrdy J; Brynychova V; Mrhalova M; Kodet R; Rob L; Pluta M; Gut I; Soucek P; Vaclavikova R

**INSTITUCIÓN / INSTITUTION:** - Toxicogenomics Unit, National Institute of Public Health, Prague, Czech Republic.

**RESUMEN / SUMMARY:** - Taxane and platinum-based chemotherapy regimens are standard treatment for advanced ovarian carcinoma. Expression levels of putative markers of taxane resistance in carcinoma tissues and paired peritoneal samples (n=55) and in 16 samples of ovaries without signs of carcinoma were compared with clinical data and the patients' time to progression. KIF14, PRC1, CIT and ABCC1 genes were significantly overexpressed in carcinomas when compared with normal ovarian tissues,

while ABCB1 and CASP9 expression was decreased. Associations of protein expression of the proliferation marker Ki-67 with KIF14, PRC1, ABCB1 and CASP2 were found. Lastly, it was discovered that ABCB1 and CASP2 levels associated with FIGO stage and that the CIT level associated with the time to progression of ovarian carcinoma patients ( $P < 0.0001$ ). In conclusion, ABCB1, CASP2, KIF14, PRC1 and CIT genes seem to associate with surrogate markers of ovarian carcinoma progression and CIT gene associates with therapy outcome.

[262]

**TÍTULO / TITLE:** - Clinicopathological and prognostic significance of myofibrillogenesis regulator-1 protein expression in pancreatic ductal adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0862-](http://1007/s13277-013-0862-4)

[4](#)

**AUTORES / AUTHORS:** - Zhao CY; Guo ZJ; Dai SM; Zhang Y; Zhou JJ

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Wuxi No. 4 People's Hospital, Wuxi Hospital of Oncology, No. 200, Huihe Road, Wuxi, 214062, China, [zhaochangyong2001@163.com](mailto:zhaochangyong2001@163.com).

**RESUMEN / SUMMARY:** - Myofibrillogenesis regulator-1 (MR-1) expression was detected in different malignancies and is associated with poor prognosis. However, its role in pancreatic ductal adenocarcinoma (PDAC) has not been fully elucidated. Thus, the aim of this study was to investigate the association of MR-1 expression with clinicopathologic features and prognosis in patients with PDAC. Immunohistochemistry was performed to investigate the protein expression of MR-1 and epithelial (E)-cadherin in 87 patients with PDAC. Results showed that MR-1 expression was correlated with histologic grade, tumor stage, and lymph node metastasis (all  $P < 0.05$ ). In addition, MR-1 expression showed a significant inverse correlation with E-cadherin expression ( $P = 0.002$ ). Furthermore, the variables associated with prognosis were analyzed by Cox's proportional hazards model. Kaplan-Meier analysis was used to plot survival curves according to different expression levels of MR-1. Kaplan-Meier analysis revealed that MR-1 expression was significantly associated with worse disease-free survival (DFS) and overall survival (OS) rates in patients with PDAC (both  $P < 0.001$ ). Finally, multivariate analysis demonstrated that MR-1 expression, together with histologic grade, tumor stage, lymph node metastasis, was an independent prognostic factor for both DFS and OS rates in patients with PDAC. MR-1 overexpression was tightly associated with more aggressive tumor behavior and a poor prognosis, indicating that MR-1 is a valuable molecular biomarker for PDAC progression.

[263]

**TÍTULO / TITLE:** - Effect of soluble factors derived from oral cancer cells on the production of interferon-gamma from peripheral blood mononuclear cells following stimulation with OK-432.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 May 17. doi: 10.3892/or.2013.2480.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2480](#)

**AUTORES / AUTHORS:** - Ohe G; Sasai A; Uchida D; Tamatani T; Nagai H; Miyamoto Y

**INSTITUCIÓN / INSTITUTION:** - Department of Oral Surgery, Subdivision of Molecular Oral Medicine, Division of Integrated Sciences of Translational Research, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima 770-8504, Japan.

**RESUMEN / SUMMARY:** - The streptococcal antitumor agent OK-432 is commonly used as an immunopotentiator for immunotherapy in various types of malignant tumors including oral cancer. It has been demonstrated that OK-432 elicits an antitumor effect by stimulating immunocompetent cells, thereby inducing multiple cytokines including interferon (IFN)-gamma, interleukin (IL)-2 and IL-12. Serum concentrations of IFN-gamma in patients with oral cancer were examined 24 h after administration of OK-432. Serum concentrations of IFN-gamma in patients with advanced cancer were significantly lower than those in patients with early cancer. These results suggested that some soluble factors produced by cancer cells may inhibit IFN-gamma production with OK-432. Thus, in the present study, an in vitro simulation model was established for the immune status of patients with oral cancer by adding conditioned medium (CM) derived from oral cancer cell lines into a culture of peripheral blood mononuclear cells (PBMCs) derived from a healthy volunteer. We investigated whether soluble factors derived from oral cancer cells affected IFN-gamma production from PBMCs following stimulation with OK-432. PBMCs stimulated with OK-432 produced a large amount of IFN-gamma; however, both IFN-gamma production and cytotoxic activity from PBMCs induced by OK-432 were inhibited by the addition of CM in a dose-dependent manner. In order to examine these inhibitory effects against IFN-gamma production, the contribution of inhibitory cytokines such as IL-4, IL-6, IL-10, transforming growth factor-beta and vascular endothelial growth factor was investigated. However, neutralization of these inhibitory cytokines did not recover IFN-gamma production inhibited by CM. These results indicated that unknown molecules may inhibit IFN-gamma production from PBMCs following stimulation with OK-432.

[264]

**TÍTULO / TITLE:** - DNA-Damaging Agents in Cancer Chemotherapy: Serendipity and Chemical Biology.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chem Biol. 2013 May 23;20(5):648-59. doi: 10.1016/j.chembiol.2013.04.007.

●●Enlace al texto completo (gratis o de pago)

[1016/j.chembiol.2013.04.007](http://1016/j.chembiol.2013.04.007)

**AUTORES / AUTHORS:** - Cheung-Ong K; Giaever G; Nislow C

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Genetics and the Donnelly Centre, University of Toronto, Toronto, ON M5S 3E1, Canada.

**RESUMEN / SUMMARY:** - DNA-damaging agents have a long history of use in cancer chemotherapy. The full extent of their cellular mechanisms, which is essential to balance efficacy and toxicity, is often unclear. In addition, the use of many anticancer drugs is limited by dose-limiting toxicities as well as the development of drug resistance. Novel anticancer compounds are continually being developed in the hopes of addressing these limitations; however, it is essential to be able to evaluate these compounds for their mechanisms of action. This review covers the current DNA-damaging agents used in the clinic, discusses their limitations, and describes the use of chemical genomics to uncover new information about the DNA damage response network and to evaluate novel DNA-damaging compounds.

[265]

**TÍTULO / TITLE:** - Mangiferin exerts antitumor activity in breast cancer cells by regulating matrix metalloproteinases, epithelial to mesenchymal transition, and beta-catenin signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Toxicol Appl Pharmacol. 2013 May 22. pii: S0041-008X(13)00209-3. doi: 10.1016/j.taap.2013.05.011.

●●Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.05.011](http://1016/j.taap.2013.05.011)

**AUTORES / AUTHORS:** - Li H; Huang J; Yang B; Xiang T; Yin X; Peng W; Cheng W; Wan J; Luo F; Li H; Ren G

**INSTITUCIÓN / INSTITUTION:** - Molecular Oncology and Epigenetics Laboratory, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

**RESUMEN / SUMMARY:** - Although mangiferin which is a naturally occurring glucosylxanthone has exhibited promising anticancer activities, the detailed molecular mechanism of mangiferin on cancers still remains enigmatic. In this study, the anticancer activity of mangiferin was evaluated in breast cancer cell line-based in vitro and in vivo models. We showed that mangiferin treatment resulted in decreased cell viability and suppression of metastatic potential in breast cancer cells. Further mechanistic investigation revealed that mangiferin induced decreased matrix metalloproteinase (MMP)-7 and -9, and reversal of epithelial-mesenchymal transition (EMT). Moreover, it was demonstrated that

mangiferin significantly inhibited the activation of beta-catenin pathway. Subsequent experiments showed that inhibiting beta-catenin pathway might play a central role in mangiferin-induced anticancer activity through modulation of MMP-7 and -9, and EMT. Consistent with these findings in vitro, the antitumor potential was also verified in mangiferin-treated MDA-MB-231 xenograft mice where significantly decreased tumor volume, weight and proliferation, and increased apoptosis were obtained, with lower expression of MMP-7 and -9, vimentin and active beta-catenin, and higher expression of E-cadherin. Taken together, our study suggests that mangiferin might be used as an effective chemopreventive agent against breast cancer.

[266]

**TÍTULO / TITLE:** - SPROUTY2 is a beta-catenin and FOXO3a target gene indicative of poor prognosis in colon cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncogene. 2013 Apr 29. doi: 10.1038/onc.2013.140.

●●Enlace al texto completo (gratis o de pago) [1038/onc.2013.140](#)

**AUTORES / AUTHORS:** - Ordonez-Moran P; Irmisch A; Barbachano A; Chicote I; Tenbaum S; Landolfi S; Tabernero J; Huelsken J; Munoz A; Palmer HG

**INSTITUCIÓN / INSTITUTION:** - 1] Instituto de Investigaciones Biomedicas 'Alberto Sols', Consejo Superior de Investigaciones Cientificas-Universidad Autonoma de Madrid, Madrid, España [2] Swiss Institute for Experimental Cancer Research, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland.

**RESUMEN / SUMMARY:** - SPROUTY2 (SPRY2) is an intracellular regulator of receptor tyrosine kinase signaling involved in cell growth, differentiation and tumorigenesis. Here, we show that SPRY2 is a target gene of the Wnt/beta-catenin pathway that is abnormally activated in more than 90% of colon carcinomas. In human colon cancer cells, SPRY2 expression is induced by beta-catenin in co-operation with the transcription factor FOXO3a instead of lymphoid enhancer factor/T-cell factor proteins. We found binding of beta-catenin to the SPRY2 promoter at FOXO3a response elements. In vivo, cells marked by nuclear beta-catenin and FOXO3a express SPRY2 in proliferative epithelial tissues, such as intestinal mucosa and epidermis. Consistently, inducible beta-catenin deletion in mice reduced Spry2 expression in the small intestine. Moreover, SPRY2 protein expression correlated with nuclear beta-catenin and FOXO3a colocalization in human colon carcinomas. Importantly, the amount of SPRY2 protein correlated with shorter overall survival of colon cancer patients. Our data reveal SPRY2 as a novel Wnt/beta-catenin and FOXO3a target gene indicative of poor prognosis in colon cancer. Oncogene advance online publication, 29 April 2013; doi:10.1038/onc.2013.140.

[267]

**TÍTULO / TITLE:** - Alteration of the E-cadherin/beta-Catenin Complex Predicts Poor Response to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) Treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1245/s10434-013-2970-](#)

[1](#)

**AUTORES / AUTHORS:** - Yoo SB; Kim YJ; Kim H; Jin Y; Sun PL; Jheon S; Lee JS; Chung JH

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Epidermal growth factor receptor (EGFR) mutation alone may be insufficient to predict clinical outcomes in the response to EGFR-tyrosine kinase inhibitor (TKI) therapy. The secondary mutation T790 M and MET amplification are mechanisms of acquired resistance to EGFR-TKI in approximately 50 % of patients, but the remaining mechanisms are unknown. METHODS: Eight metastatic lesions and specimens from 41 non-small cell lung carcinoma (NSCLC) patients harbouring activating EGFR mutations who underwent surgical resection and EGFR-TKI therapy were available. Immunohistochemistry was used to evaluate E-cadherin, beta-catenin, and PTEN. Chromogenic in situ hybridisation and silver-enhanced in situ hybridisation were used to evaluate EGFR and MET amplification. RESULTS: Patients with E-cadherin/beta-catenin alteration showed a poor objective response rate (ORR) ( $p = 0.005$ ) and shorter overall survival ( $p = 0.059$ ). Additionally, beta-catenin alteration was associated with a poor ORR ( $p = 0.012$ ). Of the metastatic tumours, three cases (37.5 %) showed the acquisition of altered E-cadherin/beta-catenin and PTEN loss and two cases (25 %) demonstrated MET/EGFR amplification. CONCLUSIONS: Altered E-cadherin/beta-catenin expression in NSCLC harbouring EGFR mutations was associated with a poor response to EGFR-TKI. During metastatic progression, changes in E-cadherin/beta-catenin were found. These results may suggest that E-cadherin/beta-catenin alteration is related to poor TKI response and resistance.

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[268]

**TÍTULO / TITLE:** - Interobserver Agreement and Assay Reproducibility of Folate Receptor alpha Expression in Lung Adenocarcinoma: A Prognostic Marker and Potential Therapeutic Target.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Pathol Lab Med. 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [5858/arpa.2013-0039-](#)

[OA](#)

**AUTORES / AUTHORS:** - Bremer RE; Scoggin TS; Somers EB; O'Shannessy DJ; Tacha DE

**INSTITUCIÓN / INSTITUTION:** - From the Department of Research & Development, Biocare Medical LLC, Concord, California (Drs Bremer and Tacha and Ms Scoggin); and the Department of Diagnostic Development, Morphotek Inc, Exton, Pennsylvania (Ms Somers and Dr O'Shannessy).

**RESUMEN / SUMMARY:** - Context.-Lung cancer is the leading cause of cancer deaths in the United States and globally. Folate-targeted drugs are among the promising new targeted therapies for lung cancer, provided predictive biomarkers can be identified for optimal patient selection. Objective.-To evaluate the interobserver agreement and reproducibility of an immunohistochemistry assay for folate receptor alpha as a potential predictive marker for folate-targeted therapies. Design.-Immunohistochemistry using anti-folate receptor alpha antibody 26B3 was performed on formalin-fixed, paraffin-embedded tissues. The M-score, a semiquantitative measure of staining intensity and proportion of tumor cells staining, was determined for each specimen. Interobserver agreement was assessed using lung adenocarcinoma specimens stained at a single site and evaluated by 3 independent pathologists. Interinstrument reproducibility assessed 20 specimens stained by 3 different automated stainers. Interlaboratory agreement was determined on 5 specimens, repeatedly stained on each of 5 days, at 3 different study sites. Results.-Folate receptor alpha expression was identified in 39 of 54 cases of lung adenocarcinoma (72%) and 4 of 37 cases of lung squamous cell carcinoma (11%). Agreement among 3 pathologists was found in 24 of 26 cases (92%). Interinstrument reproducibility was observed in 19 of 20 cases (95%). Agreement among 3 laboratories was found for 49 of 50 specimens (98%). Conclusions.-Immunostaining of folate receptor alpha in lung adenocarcinomas is reproducible across staining platforms and among laboratories. Agreement among pathologists is achieved using a semiquantitative scoring method. An accurate and convenient method for determining folate receptor alpha expression offers a potentially invaluable tool for selecting patients for folate-targeted therapies.

[269]

**TÍTULO / TITLE:** - Prognostic significance of changes in serum thyroglobulin antibody levels of pre- and post-total thyroidectomy in thyroglobulin antibody-positive papillary thyroid carcinoma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Endocr J. 2013 Apr 12.

**AUTORES / AUTHORS:** - Tsushima Y; Miyauchi A; Ito Y; Kudo T; Masuoka H; Yabuta T; Fukushima M; Kihara M; Higashiyama T; Takamura Y; Kobayashi K; Miya A; Kikumori T; Imai T; Kiuchi T

**INSTITUCIÓN / INSTITUTION:** - Department of Breast and Endocrine Surgery, Nagoya University, Nagoya 466-8550, Japan.

**RESUMEN / SUMMARY:** - Although postoperative serum thyroglobulin (Tg) is a prognostic indicator for papillary thyroid carcinoma (PTC), it is unreliable when Tg antibody (TgAb) is positive. We evaluated the prognostic significance of changes in serum TgAb levels of pre- and post-total thyroidectomy in TgAb-positive PTC patients. We reviewed our medical charts of 225 TgAb-positive PTC patients in whom TgAb levels were measured before and 1-2 years after total thyroidectomy, performed between April 2002 and March 2007. We divided them into 3 groups based on changes in TgAb levels. Postoperative serum TgAb levels decreased by  $\geq 50\%$  in 181 patients (80.4%) (Group 1), by  $< 50\%$  in 22 patients (9.8%) (Group 2), and increased in 22 patients (9.8%) (Group 3). During the follow-up, 3 patients died of the disease and 14 patients had recurrences. All 3 patients who died of PTC were seen only in Groups 2 and 3. Groups 2 and 3 showed similar prognostic outcomes, thus were analyzed together as Group 2+3. Group 1 had significantly better lymph node recurrence-free survival and distant recurrence-free survival than Group 2+3 (96.9% vs. 90.5%,  $p < 0.001$ , and 98.9% vs. 90.1%,  $p = 0.004$ , respectively at 5 years). Multivariate analyses on prognostic factors revealed that classification to Group 2+3 was the strongest indicator for poor prognosis. The present results suggest that changes in TgAb levels following total thyroidectomy can be an important dynamic prognostic factor of PTC patients. Prospective periodical measurements of TgAb are necessary to confirm these findings.

[270]

**TÍTULO / TITLE:** - Progesterone receptor targeting with radiolabelled steroids: An approach in predicting breast cancer response to therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Steroid Biochem Mol Biol. 2013 May 10. pii: S0960-0760(13)00064-2. doi: 10.1016/j.jsbmb.2013.04.003.

●●Enlace al texto completo (gratis o de pago)

[1016/j.jsbmb.2013.04.003](#)

**AUTORES / AUTHORS:** - Cunha S; Gano L; Ribeiro Morais G; Thiemann T; Oliveira MC

**INSTITUCIÓN / INSTITUTION:** - Unidade de Ciências Químicas e Radiofarmacêuticas, IST/ITN, Instituto Superior Técnico, Universidade Técnica de Lisboa, Estrada Nacional 10, 2686-953 Sacavem, Portugal.

**RESUMEN / SUMMARY:** - Steroid receptors have demonstrated to be potentially useful biological targets for the diagnosis and therapy follow-up of hormonally responsive cancers. The over-expression of these proteins in human cancer cells as well as their binding characteristics provides a favourable mechanism for the localization of malignant tumours. The need for newer and more selective probes to non-invasively assess steroid receptor expression in

hormone-responsive tumours has encouraged the synthesis and the biological evaluation of several steroidal derivatives labelled with positron and gamma emitters. The physiological effects of the steroid hormone progesterone are mediated by the progesterone receptor (PR). Since PR expression is stimulated by the oestrogen receptor (ER), PR status has been considered as a biomarker of ER activity and its value for predicting and monitoring therapeutic efficacy of hormonal therapy has been studied. Imaging of PR-expressing breast cancer patients under hormonal therapy may be advantageous, since the response to therapy can be more accurately predicted after quantification of both ER and PR status. Thus, ligands for PR targeting, although much less explored than ER ligands, have gained some importance lately as potential PET and SPECT tumour imaging agents. In this review, we present a brief survey of explored approaches for progesterone targeting using radiolabelled progestins as potential clinical probes to predict responsiveness to breast cancer therapy. This article is part of a Special Issue entitled 'synthesis of steroids'.

[271]

**TÍTULO / TITLE:** - Retaining cytotoxic activity of anthrapyridone CO1 against multidrug resistant cells is related to the ability to induce concomitantly apoptosis and lysosomal death of leukaemia HL60/VINC and HL60/DOX cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pharm Pharmacol. 2013 Jun;65(6):855-67. doi: 10.1111/jphp.12042. Epub 2013 Feb 28.

●●Enlace al texto completo (gratis o de pago) [1111/jphp.12042](http://1111/jphp.12042)

**AUTORES / AUTHORS:** - Nowak R; Tarasiuk J

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, University of Szczecin, Szczecin, Poland.

**RESUMEN / SUMMARY:** - **OBJECTIVES:** The effect of anthrapyridone compound CO1 retaining cytotoxic activity against multidrug resistant (MDR) tumour cells on inducing cell death of the sensitive leukaemia HL60 cell line and its MDR sublines (HL60/VINC and HL60/DOX) was examined. **METHODS:** The effects of CO1 and the reference compound doxorubicin (DOX) on examined cells were analysed by studying their cytotoxicity, drug intracellular accumulation, cell cycle distribution, caspase-3 and caspase-8 activity, Fas expression and lysosomal integrity. **KEY FINDINGS:** CO1 was much less effective at influencing the cell cycle of examined cells than DOX a well-known antitumour drug targeting cellular DNA and causing G2/M checkpoint arrest. CO1 caused much less pronounced appearance of the sub-G1 population and oligonucleosomal DNA fragmentation, characteristic of apoptosis, compared with DOX. Significantly lower caspase-3 and caspase-8 activity was also observed in the response of these cells to CO1 compared with DOX treatment. CO1 did not change the expression of the Fas death receptor, characteristic of apoptotic pathways, on the surface of studied cells. Interestingly, the results

showed that CO1 caused lysosomal membrane permeability (LMP) of the cells, whereas DOX did not perturb the lysosomal integrity of the studied cells.  
CONCLUSIONS: The results suggest that CO1 could induce LMP-mediated cell death as a main lethal effect in a caspase-independent fashion.

[272]

**TÍTULO / TITLE:** - C-X-C motif receptor 2, endostatin and proteinase-activated receptor 1 polymorphisms as prognostic factors in NSCLC.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Mar 30. pii: S0169-5002(13)00112-8. doi: 10.1016/j.lungcan.2013.03.007.

●●Enlace al texto completo (gratis o de pago)

[1016/j.lungcan.2013.03.007](#)

**AUTORES / AUTHORS:** - Uzunoglu FG; Yavari N; Bohn BA; Nentwich MF; Reeh M; Pantel K; Perez D; Tsui TY; Bockhorn M; Mann O; Izbicki JR; Wikman H; Vashist YK

**INSTITUCIÓN / INSTITUTION:** - Department of General, Visceral and Thoracic Surgery, University Medical Center of Hamburg-Eppendorf, Germany.

**RESUMEN / SUMMARY:** - The progress of non-small cell lung cancer (NSCLC) is dependent on sufficient angiogenesis. Thrombin induced activation of proteinase-activated receptor 1 (PAR-1) on platelets leads to platelet secretion and aggregation. This influences cell survival, apoptosis and angiogenesis by the release of VEGF and Endostatin (ES), a potent angiogenesis inhibitor. Interleukin-8 (IL-8) induces tumor angiogenesis independent of the VEGF pathway through the chemokine C-X-C motif receptor 2 (CXCR-2). Our purpose was to evaluate germline polymorphisms of these potential therapy targets as prognostic markers for disease free survival (DFS) and overall survival (OS) in surgically treated NSCLC patients. In total 209 Caucasian patients, treated between 1996 and 2011, were included in this study. Genomic DNA was extracted from peripheral blood leucocytes. Genotyping of CXCR-2 +1208 C>T and +785 C>T, PAR-1 -506 Ins/del and -14 lvs A>T and ES +4349 G>A was performed by TaqMan® genotyping assays or by polymerase chain reaction (PCR) followed by capillary electrophoresis. Chi-square test, Kaplan-Meier estimator and cox regression hazard model were used to assess the prognostic value of selected polymorphisms. The PAR-1 -14 lvs A/A genotype was associated with advanced tumor stages (p=0.024) and, in univariate analysis, with shorter median OS in squamous cell lung carcinoma (SqCC, p=0.035). The CXCR-2 +1208T/T genotype was associated with aggressive tumor biology (p=0.038), and shorter DFS and OS (p=0.018, p=0.021) in NSCLC and especially in SqCC a negative predictor for DFS and OS (p=0.045, p=0.041). Genotyping of the CXCR-2 +1208 C>T polymorphism could be a useful tool to identify high-risk SqCC subgroups.

[273]

**TÍTULO / TITLE:** - Development and Binding Mode Assessment of N-[4-[2-propyn-1-yl][(6S)-4,6,7,8-tetrahydro-2-(hydroxymethyl)-4-oxo-3H-cyclopenta [g]quinazolin-6-yl]amino]benzoyl]-L-gamma-glutamyl-D-glutamic acid (BGC 945), a Novel Thymidylate Synthase Inhibitor that Targets Tumor Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Chem. 2013 May 27.

●●Enlace al texto completo (gratis o de pago) [1021/jm400490e](#)

**AUTORES / AUTHORS:** - Tochowicz A; Dalziel S; Eidam O; O'Connell J; Griner S; Finer-Moore JS; Stroud RM

**RESUMEN / SUMMARY:** - N-[4-[2-propyn-1-yl][(6S)-4,6,7,8-tetrahydro-2-(hydroxymethyl)-4-oxo-3H-cyclopenta [g]quinazolin-6-yl]amino]benzoyl]-L-gamma-glutamyl-D-glutamic acid 1 (BGC 945, now known as ONX 0801), is a small molecule thymidylate synthase (TS) inhibitor discovered at the Institute of Cancer Research in London. It is licensed by Onyx Pharmaceuticals and is in Phase 1 clinical studies. It is a novel antifolate drug resembling TS inhibitors plevitrexed and raltitrexed that combines enzymatic inhibition of thymidylate synthase with alpha-folate receptor-mediated targeting of tumor cells. Thus, it has potential for efficacy with lower toxicity due to selective intracellular accumulation through alpha-folate receptor (alpha-FR) transport. The alpha-FR, a cell-surface receptor glycoprotein, which is over expressed mainly in ovarian and lung cancer tumors, has an affinity for 1 similar to that for its natural ligand, folic acid. This study describes a novel synthesis of 1, an X-ray crystal structure of its complex with Escherichia coli TS and 2'-deoxyuridine-5'-monophosphate, and a model for a similar complex with human TS.

[274]

**TÍTULO / TITLE:** - Novel Antitumor Agent, Trilacunary Keggin-Type Tungstobismuthate, Inhibits Proliferation and Induces Apoptosis in Human Gastric Cancer SGC-7901 Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Inorg Chem. 2013 May 6;52(9):5119-27. doi: 10.1021/ic400019r. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1021/ic400019r](#)

**AUTORES / AUTHORS:** - Wang L; Zhou BB; Yu K; Su ZH; Gao S; Chu LL; Liu JR; Yang GY

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Synthesis of Functional Materials and Green Catalysis Colleges of Heilongjiang Province, Department of Chemical Engineering, Harbin Normal University, Harbin, Heilongjiang 150025, People's Republic of China.

**RESUMEN / SUMMARY:** - A new one-dimensional chain-like compound of tungstobismuthate, [(W(OH)<sub>2</sub>)<sub>2</sub>

(Mn(H<sub>2</sub>O)<sub>3</sub>)<sub>2</sub>(Na<sub>3</sub>(H<sub>2</sub>O)<sub>14</sub>)(BiW<sub>9</sub>O<sub>33</sub>)<sub>2</sub>](Himi)<sub>2</sub>.16H<sub>2</sub>O (1) (imi = iminazole), has been synthesized in aqueous solution. The structure of 1 was identified by elemental analysis, IR, thermogravimetry (TG), X-ray photoelectron spectroscopy (XPS), (183)W-NMR, and single crystal X-ray diffraction. To investigate the inhibitory effect of 1 on human gastric adenocarcinoma SGC-7901 cells, cell proliferation and apoptosis initiation were examined by MTT assay (MTT = 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazoliumbromide), flow cytometry, nuclear staining, transmission electron microscopy, single cell gel electrophoresis, DNA fragmentation, and Western blotting. The results showed that 1 inhibited cell proliferation and induced apoptosis in SGC-7901 cells in dose-dependent manner. In addition, 1 also decreased the expression of bcl-2 protein and nuclear factor-kappaB p65 protein in SGC-7901 cells. And expression of bcl-2 protein exhibits a decreasing trend with increase of concentration of 1. Thus, 1 possessed a potential antitumor activity in SGC-7901 cells. This suggests that polyoxotungstates will provide a promising and novel antitumor agent in prevention and treatment of gastric adenocarcinoma.

[275]

**TÍTULO / TITLE:** - 6,7-Dimethoxy-3-(3-methoxyphenyl)isoquinolin-1-amine induces mitotic arrest and apoptotic cell death through the activation of spindle assembly checkpoint in human cervical cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bgt133](#)

**AUTORES / AUTHORS:** - Chung KS; Choi HE; Shin JS; Cho YW; Choi JH; Cho WJ; Lee KT

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Biochemistry.

**RESUMEN / SUMMARY:** - Previously, we reported that 6,7-dimethoxy-3-(3-methoxyphenyl)isoquinolin-1-amine (CWJ-082) has potent cytotoxic effects on various cancer cells, but the underlying molecular mechanism responsible was not determined. In the present study, CWJ-082 caused cervical cancer cell cycle arrest at the G<sub>2</sub>/M phase and subsequent caspase-dependent apoptosis. The mitotic arrest caused by CWJ-082 found to be due to increases in the activation of cyclin-dependent kinase 1/cyclin B1 complex and the phosphorylation of histone H3. In addition, CWJ-082 induced the phosphorylation of BubR1 and the association between mitotic arrest deficient 2 (Mad2) and cell division cycle protein 20. These findings suggested that CWJ-082 activated the mitotic spindle checkpoint. Furthermore, knockdown of the spindle checkpoint proteins BubR1 or Mad2 using specific small interfering RNAs significantly reduced CWJ-082-induced mitotic cell accumulation and apoptosis. In addition, CWJ-082 induced the appearance of spindle abnormalities by inducing alpha-tubulin polymerization. In BALB/cnu/nu mice bearing a HeLa xenograft, CWJ-082 significantly inhibited tumor growth. Taken

together, these results suggest that CWJ-082 inhibits cell growth via mitotic arrest by activating the mitotic spindle checkpoint and by inducing alpha-tubulin polymerization and that these events ultimately lead to the apoptosis of human cervical cancer cells and inhibit tumor growth in HeLa xenograft mice.

[276]

**TÍTULO / TITLE:** - Intraoperative sentinel node biopsy by one-step nucleic acid amplification (OSNA) avoids axillary lymphadenectomy in women with breast cancer treated with neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Surg Oncol. 2013 May 24. pii: S0748-7983(13)00373-9. doi: 10.1016/j.ejso.2013.05.002.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejso.2013.05.002](http://1016/j.ejso.2013.05.002)

**AUTORES / AUTHORS:** - Navarro-Cecilia J; Duenas-Rodriguez B; Luque-Lopez C; Ramirez-Exposito MJ; Martinez-Ferrol J; Ruiz-Mateas A; Urena C; Carrera-Gonzalez MP; Mayas MD; Martinez-Martos JM

**INSTITUCIÓN / INSTITUTION:** - Breast Pathology Unit, Department of Surgery, Hospital Complex of Jaen, Av. Ejercito Español, 10, Jaen 23 007, España.

**RESUMEN / SUMMARY:** - BACKGROUND: There is no evidence that supports the recommendation of sentinel lymph node biopsy (SLNB) in patients with breast cancer who have treated with neoadjuvant chemotherapy (NAC) to downsize tumors in order to allow breast conservation surgery, because NAC induces anatomical alterations of the lymphatic drainage. We evaluated the effectiveness of SLNB using intraoperative one-step nucleic acid amplification (OSNA) method to detect microscopic metastases or isolated tumor cells after NAC in patients with clinically negative axillary nodes at initial presentation. PATIENTS AND METHODS: We evaluated in patients with breast cancer and clinically negative axilla at presentation, the effectiveness of SLNB by OSNA after NAC (71 patients) or prior to NAC (40 patients). RESULTS: The rate of SLN identification was 100% in both groups. 17 women with SLNB prior to systemic treatment showed positive nodes (14 macrometastases and 3 micrometastases), and positive SLNB were detected in 15 women with SLNB after NAC, which were 14 macrometastases and 1 micrometastase. The negative predictive value of ultrasonography was 57.5% in patients with SLNB prior to neoadjuvant therapy and 78.9% in patients with chemotherapy followed by SLNB. CONCLUSIONS: Intraoperative SLNB using OSNA in women with clinically negative axillary lymph nodes at initial presentation who received NAC could predict axillary status with high accuracy. Also it allows us to take decisions about the indication or not to perform an axillary dissection at the moment, thus avoiding delay in the administration of chemotherapy and benefiting the patients from a single surgical procedure.

[277]

**TÍTULO / TITLE:** - Rapamycin Sensitizes Glucocorticoid Resistant Acute Lymphoblastic Leukemia CEM-C1 Cells to Dexamethasone Induced Apoptosis through both mTOR Suppression and Up-Regulation and Activation of Glucocorticoid Receptor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Environ Sci. 2013 May;26(5):371-81. doi: 10.3967/0895-3988.2013.05.006.

●●Enlace al texto completo (gratis o de pago) [3967/0895-3988.2013.05.006](#)

**AUTORES / AUTHORS:** - Guo X; Zhou CY; Li Q; Gao J; Zhu YP; Gu L; Ma ZG

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Hematology/Oncology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: To explore the role of glucocorticoid (GC) receptor (GR) in rapamycin's reversion of GC resistance in human GC-resistant T-acute lymphoblastic leukemia (ALL) CEM-C1 cells. METHODS: CEM-C1 cells were cultured in vitro and treated with rapamycin at different concentrations with or without 1  $\mu\text{mol/L}$  dexamethasone (Dex). 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) test was performed to assess cell proliferation. The cell cycle and cell apoptosis were analyzed by flow cytometry. The expression of GR $\alpha$  mRNA was determined by real-time quantitative RT-PCR. The expression of GR, p-70S6K, Mcl-1, and Bim proteins was detected by Western blot. RESULTS: When incubated with rapamycin at different concentrations, CEM-C1 cells showed significant growth inhibition in a time- and concentration-dependent manner. The growth inhibition was synergistically increased when CEM-C1 cells were treated with rapamycin plus 1  $\mu\text{mol/L}$  Dex. CEM-C1 cells treated with rapamycin alone showed no apparent apoptosis, and were arrested at G0/G1 phase. After the treatment with Dex plus rapamycin, CEM-C1 cells demonstrated apparent apoptosis and increased the cell cycle arrested at G0/G1 phase. Rapamycin combined with Dex up-regulated GR $\alpha$ , phosphorylated GR(p-GR), and pro-apoptotic protein Bim-EL in CEM-C1 cells, but inhibited the expression of p-p70S6K, a downstream target protein of mTOR (mammalian target of rapamycin). CONCLUSION: After the treatment with rapamycin plus Dex, Dex resistant CEM-C1 cells induce growth inhibition and apoptosis. The underlying mechanism may involve inhibition of the mTOR signaling pathway and also be associated with up-regulation of GR expression and activation of GC-GR signaling pathway.

[278]

**TÍTULO / TITLE:** - Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: A Gynecologic Oncology Group study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Apr 8. pii: S0090-8258(13)00214-X. doi: 10.1016/j.ygyno.2013.04.001.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.04.001](#)

**AUTORES / AUTHORS:** - Landrum LM; Java J; Mathews CA; Lanneau GS Jr; Copeland LJ; Armstrong DK; Walker JL

**INSTITUCIÓN / INSTITUTION:** - University of Oklahoma Health Sciences Center, Section of GYN Oncology, Oklahoma City, OK, USA. Electronic address: [Lisa-landrum@ouhsc.edu](mailto:Lisa-landrum@ouhsc.edu).

**RESUMEN / SUMMARY:** - OBJECTIVES: To determine prognostic factors for survival in ovarian cancer patients treated with intraperitoneal (IP) chemotherapy using ancillary data from cooperative group clinical trials. METHODS: Data were collected from 428 patients with stage III ovarian cancer who underwent optimal surgical cytoreduction (<1cm) followed by IP paclitaxel/platinum chemotherapy. Primary endpoints were progression free survival (PFS) and overall survival (OS). Potential prognostic variables were included in Cox proportional hazard regression models. Multivariate analysis was conducted to identify independent prognostic factors. RESULTS: Median PFS was 24.9months (95% CI, 23.0-29.2) and median OS was 61.8months (95% CI, 55.5-69.8). Predictors for PFS were histology, surgical stage and residual disease. Age, histology, and residual disease were prognostic for OS. There were no differences in the hazard ratio for death or progression between patients with positive, negative, or unknown lymph node status. For patients receiving IP chemotherapy (n=428), 36% of patients had no residual disease with median PFS of 43.2months (95% CI 32.5-60.4) and median OS of 110months (95% CI, 60.0-161.3). CONCLUSIONS: Age, histology, and extent of residual disease were predictors of OS in stage III patients treated with IP chemotherapy following optimal cytoreduction. Patients with no residual disease following primary surgery that are treated with adjuvant platinum based IP chemotherapy have survival measures that exceed any rates previously seen in this population.

[279]

**TÍTULO / TITLE:** - Treatment of Triple-Negative Breast Cancer Using Anti-EGFR-Directed Radioimmunotherapy Combined with Radiosensitizing Chemotherapy and PARP Inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Nucl Med. 2013 Jun;54(6):913-21. doi: 10.2967/jnumed.112.111534. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago)

[2967/jnumed.112.111534](#)

**AUTORES / AUTHORS:** - Al-Ejeh F; Shi W; Miranda M; Simpson PT; Vargas AC; Song S; Wiegman AP; Swarbrick A; Welm AL; Brown MP; Chenevix-Trench G; Lakhani SR; Khanna KK

**INSTITUCIÓN / INSTITUTION:** - Signal Transduction Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia.

**RESUMEN / SUMMARY:** - Triple-negative breast cancer (TNBC) is associated with poor survival. Chemotherapy is the only standard treatment for TNBC. The prevalence of BRCA1 inactivation in TNBC has rationalized clinical trials of poly(adenosine diphosphate ribose) polymerase (PARP) inhibitors. Similarly, the overexpression of epidermal growth factor receptor (EGFR) rationalized anti-EGFR therapies in this disease. However, clinical trials using these 2 strategies have not reached their promise. In this study, we used EGFR as a target for radioimmunotherapy and hypothesized that EGFR-directed radioimmunotherapy can deliver a continuous lethal radiation dose to residual tumors that are radiosensitized by PARP inhibitors and chemotherapy.

**METHODS:** We analyzed EGFR messenger RNA in published gene expression array studies and investigated EGFR protein expression by immunohistochemistry in a cohort of breast cancer patients to confirm EGFR as a target in TNBC. Preclinically, using orthotopic and metastatic xenograft models of EGFR-positive TNBC, we investigated the effect of the novel combination of (177)Lu-labeled anti-EGFR monoclonal antibody, chemotherapy, and PARP inhibitors on cell death and the survival of breast cancer stem cells. **RESULTS:** In this first preclinical study of anti-EGFR radioimmunotherapy in breast cancer, we found that anti-EGFR radioimmunotherapy is safe and that TNBC orthotopic tumors and established metastases were eradicated in mice treated with anti-EGFR radioimmunotherapy combined with chemotherapy and PARP inhibitors. We showed that the superior response to this triple-agent combination therapy was associated with apoptosis and eradication of putative breast cancer stem cells. **CONCLUSION:** Our data support further preclinical investigations toward the development of combination therapies using systemic anti-EGFR radioimmunotherapy for the treatment of recurrent and metastatic TNBC.

[280]

**TÍTULO / TITLE:** - Transcriptome Profiling Identifies HMGA2 as a Novel Gene in Melanoma Progression and Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Invest Dermatol. 2013 Apr 30. doi: 10.1038/jid.2013.197.

●●Enlace al texto completo (gratis o de pago) [1038/jid.2013.197](https://doi.org/10.1038/jid.2013.197)

**AUTORES / AUTHORS:** - Raskin L; Fullen DR; Giordano TJ; Thomas DG; Frohm ML; Cha KB; Ahn J; Mukherjee B; Johnson TM; Gruber SB

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Division of Epidemiology, Vanderbilt University, Nashville, TN, USA.

**RESUMEN / SUMMARY:** - The genetic alterations contributing to melanoma pathogenesis are incompletely defined, and few independent prognostic features have been identified beyond the clinicopathological characteristics of the primary tumor. We used transcriptome profiling of 46 primary melanomas, 12 melanoma metastases, and 16 normal skin samples to find novel genes associated with melanoma development and progression. Results were confirmed using immunohistochemistry and real-time PCR and replicated in an independent set of 330 melanomas using AQUA analysis of tissue microarray. Transcriptome profiling revealed that transcription factor HMGA2, previously unrecognized in melanoma pathogenesis, is significantly upregulated in primary melanoma and metastases (P-values=1.2 x 10<sup>-7</sup> and 9 x 10<sup>-5</sup>) compared to normal skin. HMGA2 overexpression is associated with BRAF/NRAS mutations (P=0.0002). Cox-proportional hazard regression model and log-rank test showed that HMGA2 is independently associated with DFS (hazard ratio (HR)=6.3, 95% confidence interval (CI)=1.8-22.3, P=0.004), OS (stratified log-rank P=0.008), and DMFS (HR=6.4, 95%CI=1.4-29.7, P=0.018) after adjusting for AJCC stage and age at diagnosis. Survival analysis in an independent replication tissue microarray (TMA) of 330 melanomas confirmed the association of HMGA2 expression with OS (P=0.0211). Our study implicates HMGA2 in melanoma progression and demonstrates that HMGA2 overexpression can serve as an independent predictor of survival in melanoma. Journal of Investigative Dermatology accepted article preview online, 30 April 2013; doi:10.1038/jid.2013.197.

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[281]

**TÍTULO / TITLE:** - Connexin43 confers Temozolomide resistance in human glioma cells by modulating the mitochondrial apoptosis pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neuropharmacology. 2013 May 18. pii: S0028-3908(13)00211-6. doi: 10.1016/j.neuropharm.2013.05.002.

●●Enlace al texto completo (gratis o de pago)

[1016/j.neuropharm.2013.05.002](http://1016/j.neuropharm.2013.05.002)

**AUTORES / AUTHORS:** - Gielen PR; Aftab Q; Ma N; Chen VC; Hong X; Lozinsky S; Naus CC; Sin WC

**INSTITUCIÓN / INSTITUTION:** - Department of Cellular and Physiological Science, Life Science Institute, University of British Columbia, 2350 Health Science Mall, Vancouver, BC V6T 1Z3, Canada; Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, Netherlands.

**RESUMEN / SUMMARY:** - Glioblastoma multiforme (GBM) is the most aggressive astrocytoma, and therapeutic options are generally limited to surgical resection,

radiotherapy, and Temozolomide (TMZ) chemotherapy. TMZ is a DNA alkylating agent that causes DNA damage and induces cell death. Unfortunately, glioma cells often develop resistance to TMZ treatment, with DNA de-methylation of the MGMT promoter identified as the primary reason. However, the contributions from proteins that normally protect cells against cytotoxic stress in TMZ-induced apoptosis have not been extensively explored. Here, we showed that increasing the level of the gap junction protein, Cx43, in human LN18 and LN229 glioma cells enhances resistance to TMZ treatment while knockdown of Cx43 in these same cells sensitizes them to TMZ treatment. By expressing a channel-dead or a C-terminal truncation mutant of Cx43, we show that Cx43-mediated TMZ resistance involves both channel dependent and independent functions. Expression of Cx43 in LN229 cells decreases TMZ-induced apoptosis, as determined by Annexin V staining. Cx43-mediated chemoresistance appears to be acting via a mitochondrial apoptosis pathway as manifested by the reduction in Bax/Bcl-2 ratio and the release of cytochrome C. Our findings highlight additional mechanisms and proteins that contribute to TMZ resistance, and raise the possibility of increasing TMZ efficiency by targeting Cx43 protein. This article is part of a Special Issue entitled 'Connexin based channels'.

[282]

**TÍTULO / TITLE:** - Arylpiperazine-mediated activation of Akt protects SH-SY5Y neuroblastoma cells from 6-hydroxydopamine-induced apoptotic and autophagic death.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neuropharmacology. 2013 May 3;72C:224-235. doi: 10.1016/j.neuropharm.2013.04.037.

●●Enlace al texto completo (gratis o de pago)

[1016/j.neuropharm.2013.04.037](#)

**AUTORES / AUTHORS:** - Tovilovic G; Zogovic N; Soskic V; Schratzenholz A; Kostic-Rajacic S; Misirkic-Marjanovic M; Janjetovic K; Vucicevic L; Arsin K; Harhaji-Trajkovic L; Trajkovic V

**INSTITUCIÓN / INSTITUTION:** - Institute for Biological Research, University of Belgrade, Despota Stefana Blvd. 142, 11000 Belgrade, Serbia.

**RESUMEN / SUMMARY:** - We investigated the ability of 19 recently synthesized arylpiperazine compounds to protect human SH-SY5Y neuroblastoma cells from the neurotoxin 6-hydroxydopamine (6-OHDA). The compound with the most potent neuroprotective action was N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-picolinamide (6b), which reduced 6-OHDA-induced apoptotic death through stabilization of mitochondrial membrane and subsequent prevention of superoxide production, caspase activation and DNA fragmentation. 6-OHDA-triggered autophagic response was also reduced by 6b, which prevented inactivation of the main autophagy repressor mTOR, upregulation of

proautophagic beclin-1, conversion of microtubule-associated protein 1 light chain 3 (LC3)-I to autophagosome-associated LC3-II, as well as intracytoplasmic acidification induced by 6-OHDA. The inhibition of autophagy using LC3beta gene silencing or pharmacological autophagy blockers 3-methyladenine or bafilomycin A1, mimicked the cytoprotective effect of 6b. While the treatment with 6b had no effect on the phosphorylation of proapoptotic MAP kinases ERK and JNK, it markedly increased the phosphorylation of the prosurvival kinase Akt in 6-OHDA-treated cells. Akt inhibitor DEBC or RNA interference-mediated Akt silencing reduced the ability of 6b to block 6-OHDA-triggered apoptotic and autophagic responses, thus confirming their dependency on Akt activation. The cytoprotective effect of 6b was also observed in 6-OHDA-treated neuronal PC12 cells, but not in SH-SY5Y or PC12 cells exposed to 1-methyl-4-phenylpyridinium, indicating that the observed neuroprotection was dependent on the cytotoxic stimulus. Because of the ability to prevent 6-OHDA induced apoptotic/autophagic cell death through activation of Akt, the investigated arylpiperazines could be potential candidates for treatment of neurodegenerative diseases.

[283]

**TÍTULO / TITLE:** - Membrane Localized Iridium(III) Complex Induces Endoplasmic Reticulum Stress and Mitochondria-Mediated Apoptosis in Human Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Chem. 2013 May 9;56(9):3636-44. doi: 10.1021/jm4001665. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1021/jm4001665](http://1021/jm4001665)

**AUTORES / AUTHORS:** - Cao R; Jia J; Ma X; Zhou M; Fei H

**INSTITUCIÓN / INSTITUTION:** - Division of Nanobiomedicine, Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences, 398 Ruoshui Road, Suzhou Industrial Park, Suzhou, Jiangsu, 215123, P. R. China.

**RESUMEN / SUMMARY:** - The cellular behavior and toxicity effect of organometallic complexes depend largely on their peripheral ligands. In this study, we have synthesized a series of novel luminescent cationic iridium(III) complexes by tuning the ancillary N(wedge)N ligand based on a structure [Ir(ppy)2(N(wedge)N)](+) (ppy = 1-phenyl-pyridine; N(wedge)N = 2,2'-bipyridine (bpy, 1) or phenanthroline (phen, 2) or 4,7-diphenyl-1,10-phenanthroline (DIP, 3)). As the size of coordinated N(wedge)N ligand increases, absorbance/emission efficiency, quantum yields, lipophilicity, and cell uptake rates of the complexes also increase, in a general order: 3 > 2 > 1. All three complexes display anticancer activity, with 3 exhibiting the highest cellular uptake efficiency and the greatest cytotoxic activities in several cancer cell lines with IC50s lower than that of cisplatin. Because of its strong hydrophobic nature, the death inducer 3 was found to accumulate favorably to endoplasmic

reticulum (ER) and to cause ER stress in cells. The fast cytosolic release of calcium from stressed ER disturbed the morphology and function of mitochondria, initiating an intrinsic apoptotic pathway. Understanding of the cell death mechanism would help further structure-activity optimization on these novel Ir(III) complexes as emerging cancer therapeutics.

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[284]

**TÍTULO / TITLE:** - Methylene blue-mediated photodynamic therapy enhances apoptosis in lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 May 24. doi: 10.3892/or.2013.2494.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2494](#)

**AUTORES / AUTHORS:** - Lim EJ; Oak CH; Heo J; Kim YH

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Biology and Immunology, Kosin University College of Medicine, Busan, Republic of Korea.

**RESUMEN / SUMMARY:** - Combined treatment with a photosensitizer and iodide laser [photodynamic therapy (PDT)] has improved the outcome of various cancers. In this study, we investigated the effects of using the photosensitizer methylene blue (MB) in PDT in human lung adenocarcinoma cells. We found that MB enhances PDT-induced apoptosis in association with downregulation of anti-apoptotic proteins, reduced mitochondrial membrane potential (MMP), increased phosphorylation of the mitogen-activated protein kinase (MAPK) and the generation of reactive oxygen species (ROS). In MB-PDT-treated A549 cells, we observed PARP cleavage, procaspase-3 activation, downregulation of the anti-apoptotic proteins Bcl-2 and Mcl-1, and the reduction of mitochondrial membrane potential (MMP). Western blot data showed that phosphorylation of p38 was increased in MB-PDT-treated A549 cells, indicating that several signaling molecules participate in the apoptotic cascade. Our data also showed that apoptotic cell death in MB-PDT-treated cells occurred through a series of steps beginning with the photochemical generation of ROS. Demonstrating the role of ROS, pretreatment of A549 cells with the antioxidant N-acetylcysteine (NAC) followed by MB-PDT resulted in increased cell viability and reduced proteolytic cleavage of PARP.

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[285]

**- CASTELLANO -**

**TÍTULO / TITLE:** Molekular zielgerichtete Therapieansätze beim Rhabdomyosarkom: Fokus auf dem Hedgehog- und Apoptose-Signalweg.

**TÍTULO / TITLE:** - Molecular Targeted Therapies for Rhabdomyosarcoma: Focus on Hedgehog and Apoptosis Signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Klin Padiatr. 2013 May;225(3):115-119. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [1055/s-0032-1331762](https://doi.org/10.5555/s-0032-1331762)

**AUTORES / AUTHORS:** - Fulda S

**INSTITUCIÓN / INSTITUTION:** - Institute for Experimental Cancer Research in Pediatrics, Goethe-University, Frankfurt a. Main, Germany.

**RESUMEN / SUMMARY:** - Dysfunction of cell death and proliferation pathways can contribute to rhabdomyosarcomagenesis, tumor progression and treatment resistance. Therefore, the identification of key signaling hubs and molecules that govern the decision between life and death of a cancer cell is expected to open new perspectives for drug discovery. For example, programmed cell death pathways can be engaged in rhabdomyosarcoma (RMS) cells by recombinant soluble proteins, monoclonal antibodies or small-molecule inhibitors. In addition, the hedgehog (Hh) cascade is often aberrantly activated in RMS and represents a promising target for therapeutic intervention. The development of molecular targeted cancer therapeutics will likely lead to more effective treatment options for patients with RMS.

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[286]

**TÍTULO / TITLE:** - Over-Expression of Mcl-1 Confers Multi-Drug Resistance While Topo IIbeta Down-Regulation Introduces Mitoxantrone-Specific Drug Resistance in Acute Myeloid Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Pharmacol. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1124/mol.113.086140](https://doi.org/10.1124/mol.113.086140)

**AUTORES / AUTHORS:** - Hermanson D; Das S; Li Y; Xing C

**INSTITUCIÓN / INSTITUTION:** - 1 University of Minnesota;

**RESUMEN / SUMMARY:** - Drug resistance is a serious challenge in cancer treatment and can be acquired through multiple mechanisms. These molecular changes may introduce varied extents of resistance to different therapies and need to be characterized for optimal therapy choice. A recently discovered small molecule, CXL017, reveals selective cytotoxicity towards drug resistant leukemia. A drug resistant AML cell line, HL60/MX2, also failed to acquire resistance to CXL017 upon chronic exposure and regained sensitivity towards standard therapies. In this study, we investigated the mechanisms responsible for HL60/MX2 cells' drug resistance and the molecular basis for its re-sensitization. Results show that the HL60/MX2 cell line has an elevated level of Mcl-1 protein relative to the parental cell line, HL60, and its re-sensitized cell line, HL60/MX2/CXL017, while it has a reduced level of topoisomerase IIbeta. Mcl-1 over-expression in HL60/MX2 cells is mainly regulated through phospho-ERK1/2 mediated Mcl-1 stabilization while the reduction of topoisomerase IIbeta in HL60/MX2 cells is controlled through genetic down-regulation. Up-regulating Mcl-1 introduces multi-drug resistance to standard therapies while its down-

regulation results in significant cell death. Down-regulating topoisomerase IIbeta confers resistance specifically to mitoxantrone, not to other topoisomerase II inhibitors. Overall, these data suggest that Mcl-1 over-expression is a critical determinant for cross-resistance to standard therapies while topoisomerase IIbeta down-regulation is specific to mitoxantrone resistance.

[287]

**TÍTULO / TITLE:** - Intrinsic breast cancer subtypes defined by estrogen receptor signalling-prognostic relevance of progesterone receptor loss.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mod Pathol. 2013 Apr 5. doi: 10.1038/modpathol.2013.60.

●●Enlace al texto completo (gratis o de pago) [1038/modpathol.2013.60](#)

**AUTORES / AUTHORS:** - Braun L; Mietzsch F; Seibold P; Schneeweiss A; Schirmacher P; Chang-Claude J; Peter Sinn H; Aulmann S

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, Heidelberg University, Heidelberg, Germany.

**RESUMEN / SUMMARY:** - The majority of luminal type breast carcinomas are slowly growing tumors with an overall favorable prognosis. However, a proportion of cases (luminal B tumors) are characterized by coactivation of growth factor receptors or non-canonical ER signaling and a poorer clinical outcome. The aim of our study was to evaluate whether the expression of proteins that are part of the ER signaling network may be used to distinguish low-risk from high-risk luminal tumors. Unsupervised hierarchical clustering of a set of proteins either involved in estrogen receptor signaling or associated with resistance to endocrine therapy was performed in a series of 443 postmenopausal breast carcinomas. Using this approach, we were able to reproduce the established classification with two distinct groups of luminal (estrogen receptor positive) tumors, one group of HER2-associated tumors and a group of triple-negative tumors. However, neither proliferation nor the expression of one or more of the ER-co-factors or resistance-associated factors, but PR-expression was identified as the most important stratifier distinguishing between the two luminal groups. In fact, not only the four identified clusters were shown to be significantly associated with patient outcome, PR-expression alone or in combination with Ki-67-stains stratified ER-positive tumors into a low-risk and a high-risk group. Our data indicate that defining luminal B tumors by the presence of high-risk criteria (loss of PR-expression or increased proliferation) provides a robust and highly significant stratification of ER-positive breast carcinomas into luminal A and B. Modern Pathology advance online publication, 5 April 2013; doi:10.1038/modpathol.2013.60.

[288]

**TÍTULO / TITLE:** - Effect of treatment with branched-chain amino acids during sorafenib therapy for unresectable hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatol Res. 2013 Apr 2. doi: 10.1111/hepr.12125.

●●Enlace al texto completo (gratis o de pago) [1111/hepr.12125](#)

**AUTORES / AUTHORS:** - Takeda H; Nishikawa H; Iguchi E; Ohara Y; Sakamoto A; Saito S; Nishijima N; Nasu A; Komekado H; Kita R; Kimura T; Osaki Y

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Osaka, Japan.

**RESUMEN / SUMMARY:** - AIM: To examine the effect of branched-chain amino acid (BCAA) therapy for patients with unresectable hepatocellular carcinoma (HCC) treated with sorafenib. METHODS: Seventy-eight subjects with unresectable HCC with a serum level of albumin of 3.5 g/dL or less treated with sorafenib were evaluated. They were classified into two groups: those receiving BCAA granules (n = 34; BCAA group) or a regular diet (n = 44; control group). We compared overall survival and administration period of sorafenib, and analyzed absolute changes in serum levels of albumin during sorafenib therapy in 41 patients who continued sorafenib therapy for 1 month or more with a follow up of more than 3 months. RESULTS: Median survival time (MST) in BCAA and control groups was 350 and 143 days (P = 0.007), respectively. Median administration period of sorafenib in the two groups was 59 and 41 days (P = 0.018). In the 41 patients described above, at 1 month, there was no significant change in the serum level of albumin between the two groups, but at 3 months, the difference in the absolute change in the serum level of albumin in the two groups reached significance (P = 0.023). In these subgroup analyses, the administration period of sorafenib as well as the MST in the BCAA group were significantly longer than those in the control group (P = 0.020 and = 0.004). CONCLUSION: BCAA treatment during sorafenib therapy in HCC patients is useful for maintaining hepatic functional reserve, which may help to avoid early discontinuance of sorafenib therapy and improve survival.

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[289]

**TÍTULO / TITLE:** - Circulating melanoma cells as a predictive biomarker.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Invest Dermatol. 2013 Jun;133(6):1460-2. doi: 10.1038/jid.2013.34.

●●Enlace al texto completo (gratis o de pago) [1038/jid.2013.34](#)

**AUTORES / AUTHORS:** - Karakousis G; Yang R; Xu X

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.

**RESUMEN / SUMMARY:** - The prognosis of patients with metastatic melanoma has improved significantly with targeted therapeutic agents and

immunotherapies. Detection of early melanoma recurrence after treatment will be beneficial to switch patients who fail on one therapy to different modalities. Circulating tumor cells (CTCs) are cancer cells released by a tumor into the peripheral blood. These cells hold potential as prognostic, predictive, and pharmacodynamic biomarkers for treatment. In this issue, Khoja et al. report that melanoma CTCs can be detected using Melcam and high molecular weight melanoma-associated antibody. They found that in 101 stage IV melanoma patients, CTC numbers ranged between 0 and 36/7.5 ml blood; 26% of the patients had  $\geq 2$  CTCs at baseline. The CTC number ( $\geq 2$  CTCs) at baseline was significantly prognostic for median overall survival (OS) in univariate and multivariate analysis. Patients receiving treatment where CTC numbers remained  $\geq 2$  CTCs during their treatment had shorter median OS than those who maintained  $< 2$  CTCs (7 vs. 10 months, hazard ratio 0.34, 95% confidence interval 0.14-0.81, log-rank test  $P=0.015$ ). The implications of this work are substantial in counseling patients about their prognosis and in helping to assess responses to systemic therapies.

[290]

**TÍTULO / TITLE:** - Farnesyltransferase inhibitor attenuates methamphetamine toxicity-induced Ras proteins activation and cell death in neuroblastoma SH-SY5Y cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neurosci Lett. 2013 Jun 17;545:138-43. doi: 10.1016/j.neulet.2013.04.034. Epub 2013 May 2.

●●Enlace al texto completo (gratis o de pago)

[1016/j.neulet.2013.04.034](#)

**AUTORES / AUTHORS:** - Pirompun N; Govitrapong P; Chetsawang B

**INSTITUCIÓN / INSTITUTION:** - Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Nakhonpathom, Thailand.

**RESUMEN / SUMMARY:** - Several lines of evidence support that methamphetamine (METH) toxicity plays a pivotal role in neurodegenerative diseases. However, the molecular mechanisms underlying METH-induced neurotoxicity are still unclear. In addition, Ras modulated death signaling has been continually reported in several cell types. In this study, intracellular Ras-dependent death signaling cascade activation was proposed to contribute to METH-induced neuronal cell degeneration in dopaminergic SH-SY5Y cultured cells. Exposure to a toxic dose of METH significantly decreased cell viability, and tyrosine hydroxylase phosphorylation, but increased c-Jun phosphorylation and active, GTP-bound Ras in cultured SH-SY5Y cells. Farnesyltransferase inhibitor, FTI-277, an inhibitor of the enzyme catalyzed the farnesylation of Ras proteins was able to diminish the toxic effects of METH on induction in cell degeneration, activation in c-Jun-N-terminal kinase cascades, and Ras activation in SH-SY5Y cells. The results of this study show that activation in Ras

signaling cascade may be implicated in the METH-induced death signaling pathway in neuroblastoma SH-SY5Y cells.

[291]

**TÍTULO / TITLE:** - Reactive Oxygen Species-Mediated Activation of AMP-Activated Protein Kinase and c-Jun N-terminal Kinase Plays a Critical Role in Beta-Sitosterol-Induced Apoptosis in Multiple Myeloma U266 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Phytother Res. 2013 May 3. doi: 10.1002/ptr.4999.

●●Enlace al texto completo (gratis o de pago) [1002/ptr.4999](#)

**AUTORES / AUTHORS:** - Sook SH; Lee HJ; Kim JH; Sohn E; Jung JH; Kim B; Kim JH; Jeong SJ; Kim SH

**INSTITUCIÓN / INSTITUTION:** - College of Korean Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-701, South Korea.

**RESUMEN / SUMMARY:** - Although beta-sitosterol has been well known to have anti-tumor activity in liver, lung, colon, stomach, breast and prostate cancers via cell cycle arrest and apoptosis induction, the underlying mechanism of anti-cancer effect of beta-sitosterol in multiple myeloma cells was never elucidated until now. Thus, in the present study, the role of reactive oxygen species (ROS) in association with AMP-activated protein kinase (AMPK) and c-Jun N-terminal kinase (JNK) pathways was demonstrated in beta-sitosterol-treated multiple myeloma U266 cells. Beta-sitosterol exerted cytotoxicity, increased sub-G1 apoptotic population and activated caspase-9 and -3, cleaved poly (ADP-ribose) polymerase (PARP) followed by decrease in mitochondrial potential in U266 cells. Beta-sitosterol promoted ROS production, activated AMPK, acetyl-CoA carboxylase (ACC) and JNK in U266 cells. Also, beta-sitosterol attenuated the phosphorylation of AKT, mammalian target of rapamycin and S6K, and the expression of cyclooxygenase-2 and VEGF in U266 cells. Conversely, AMPK inhibitor compound C and JNK inhibitor SP600125 suppressed apoptosis induced by beta-sitosterol in U266 cells. Furthermore, ROS scavenger N-acetyl L-cysteine attenuated beta-sitosterol-mediated sub-G1 accumulation, PARP cleavage, JNK and AMPK activation in U266 cells. Overall, these findings for the first time suggest that ROS-mediated activation of cancer metabolism-related genes such as AMPK and JNK plays an important role in beta-sitosterol-induced apoptosis in U266 multiple myeloma cells. Copyright © 2013 John Wiley & Sons, Ltd.

[292]

**TÍTULO / TITLE:** - Gene mutations in squamous cell NSCLC: insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EGFR-TKI treatment efficacy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1705-11.

**AUTORES / AUTHORS:** - Fiala O; Pesek M; Finek J; Benesova L; Bortlicek Z; Minarik M

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology and Radiotherapy, Medical School and Teaching Hospital Pilsen, Charles University, Prague, Czech Republic. [fiala.o@centrum.cz](mailto:fiala.o@centrum.cz)

**RESUMEN / SUMMARY:** - **BACKGROUND:** Epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene (KRAS) and phosphatidylinositide-3-kinase catalytic subunit-alpha (PIK3CA) mutations are biomarkers used for the prediction of efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in advanced non-small cell lung cancer (NSCLC). **PATIENTS AND METHODS:** In total, 223 patients with advanced-stage squamous cell NSCLC were tested; 179 patients were treated with EGFR-TKIs. Genetic testing was performed using a combination of denaturing capillary electrophoresis and direct Sanger sequencing. **RESULTS:** EGFR mutations were detected in 7.2%; KRAS mutations in 7.4% and PIK3CA mutations in 3.8% of patients. No correlation of EGFR or PIK3CA mutation status with progression-free survival (PFS) ( $p=0.425$ ;  $p=0.197$ ), nor overall survival (OS) ( $p=0.673$ ;  $p=0.687$ ), was observed. KRAS mutations correlated with shorter OS ( $p=0.039$ ), but not with PFS ( $p=0.120$ ). **CONCLUSION:** We did not observe any role of EGFR, KRAS, PIK3CA mutations in prediction of EGFR-TKIs efficacy in patients with advanced-stage squamous cell NSCLC.

[293]

**TÍTULO / TITLE:** - Cap-Translation Inhibitor, 4EGI-1, Restores Sensitivity to ABT-737 Apoptosis through Cap-Dependent and -Independent Mechanisms in Chronic Lymphocytic Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-2185](https://doi.org/10.1158/1078-0432.CCR-12-2185)

**AUTORES / AUTHORS:** - Willimott S; Beck D; Ahearne MJ; Adams VC; Wagner SD

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Cancer Studies and Molecular Medicine and MRC Toxicology Unit, University of Leicester; and Department of Haematology, University Hospitals of Leicester, Leicester, United Kingdom.

**RESUMEN / SUMMARY:** - **PURPOSE:** The lymph node microenvironment promotes resistance to chemotherapy in chronic lymphocytic leukemia (CLL), partly through induction of BCL2 family prosurvival proteins. Currently available inhibitors do not target all BCL2 family prosurvival proteins and their effectiveness is also modified by proapoptotic BCL2 homology domain 3 (BH3) only protein expression. The goal of this study was to evaluate synergy between

the eIF4E/eIF4G interaction inhibitor, 4EGI-1, and the BH3 mimetic, ABT-737. EXPERIMENTAL DESIGN: CLL cells were cultured in conditions to mimic the lymph node microenvironment. Protein synthesis and cap-complex formation were determined. Polysome association of mRNAs from BCL2 family survival genes was analyzed by translational profiling. The effects of 4EGI-1 and the BCL2/BCL2L1 antagonist, ABT-737, on CLL cell apoptosis were determined. RESULTS: Protein synthesis was increased approximately 6-fold by stromal cell/CD154 culture in a phosphoinositide 3-kinase alpha (PI3Kalpha)-specific manner and was reduced by 4EGI-1. PI3K inhibitors and 4EGI-1 also reduced cap-complex formation but only 4EGI-1 consistently reduced BCL2L1 and BCL2A1 protein levels. 4EGI-1, but not PI3K inhibitors or rapamycin, induced an endoplasmic reticulum stress response including proapoptotic NOXA and the translation inhibitor phosphorylated eIF2alpha. 4EGI-1 and ABT-737 synergized to cause apoptosis, independent of levels of prosurvival protein expression in individual patients. CONCLUSIONS: Overall protein synthesis and cap-complex formation are induced by microenvironment stimuli in CLL. Inhibition of the cap-complex was not sufficient to repress BCL2 family prosurvival expression, but 4EGI-1 inhibited BCL2A1 and BCL2L1 while inducing NOXA through cap-dependent and -independent mechanisms. 4EGI-1 and ABT-737 synergized to produce apoptosis, and these agents may be the basis for a therapeutically useful combination. Clin Cancer Res; 19(12); 1-12. ©2013 AACR.

[294]

**TÍTULO / TITLE:** - Pyrimethamine sensitizes pituitary adenomas cells to temozolomide through cathepsin B-dependent and caspase-dependent apoptotic pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Apr 6. doi: 10.1002/ijc.28199.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28199](#)

**AUTORES / AUTHORS:** - Dai C; Zhang B; Liu X; Guo K; Ma S; Cai F; Yang Y; Yao Y; Feng M; Bao X; Deng K; Jiao Y; Wei Z; Junji W; Xing B; Lian W; Wang R

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, P.R. China.

**RESUMEN / SUMMARY:** - Invasive pituitary adenomas (PAs) are generally refractory to conventional therapy and salvage treatment with temozolomide (TMZ). In addition to antiprotozoan effects, pyrimethamine (PYR) has recently shown its strong antitumor activity as an antineoplastic agent or in combination with TMZ in metastatic melanoma cells. In this study, the effects of TMZ, PYR or TMZ/PYR combination on rat/mouse PA cell lines alphaT3-1, GH3, MMQ and ATt-20 as well as GH3 xenograft tumor model were evaluated. TMZ/PYR combination synergistically inhibited proliferation, invasion and induced

apoptosis of these PA cell lines in vitro. Strikingly, combination treatment with TMZ and PYR produced synergistic antitumor activity and enhanced the survival rate of GH3 xenograft tumor models without increasing systemic side effects. In addition, TMZ/PYR induced cell cycle arrest, increased DNA damage, upregulated the expression of cathepsin B, BAX, cleaved PARP and phosphorylated histone H2AX as well as elevated caspase3/7, 8, 9 activities. The decreased expression of Bcl-2, MMP-2 and MMP-9 along with cytochrome c release from mitochondria into the cytosol were also observed in the TMZ/PYR combination group. The increase in cell apoptosis due to combination with PYR was rescued by leucovorin. These data suggest that PYR may enhance the efficacy of TMZ via triggering both cathepsin B-dependent and caspase-dependent apoptotic pathways. Therefore, combination of PYR and TMZ may provide a novel regimen for invasive PAs refractory to standard therapy and TMZ. © 2013 Wiley Periodicals, Inc.

[295]

**TÍTULO / TITLE:** - Insulin-like growth factor II messenger RNA-binding protein-3 is a valuable diagnostic and prognostic marker of intraductal papillary mucinous neoplasm.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Pathol. 2013 Apr 15. pii: S0046-8177(13)00081-6. doi: 10.1016/j.humpath.2012.12.020.

●●Enlace al texto completo (gratis o de pago)

[1016/j.humpath.2012.12.020](http://1016/j.humpath.2012.12.020)

**AUTORES / AUTHORS:** - Morimatsu K; Aishima S; Yamamoto H; Hayashi A; Nakata K; Oda Y; Shindo K; Fujino M; Tanaka M; Oda Y

**INSTITUCIÓN / INSTITUTION:** - Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan.

**RESUMEN / SUMMARY:** - Recently, various studies have shown that insulin-like growth factor II messenger RNA-binding protein-3 (IMP3) is a useful diagnostic marker for malignant lesions and a prognostic marker for poor survival in several kinds of tumors. However, the value of IMP3 as a diagnostic and prognostic marker in intraductal papillary mucinous neoplasm (IPMN) of pancreas has been unclear until now. In this study, we examined IMP3 immunohistochemical expression in 190 resection samples and 15 biopsy samples of IPMN and analyzed the value of IMP3 as a diagnostic and prognostic marker. IMP3 expression was recognized in 71.8% (28/39) of IPMNs with high-grade dysplasia and in 81.3% (26/32) of IPMNs with an associated invasive carcinoma (IPMN-IC), but it was not found in any IPMNs with low-grade dysplasia or in IPMNs with intermediate dysplasia. IMP3 expression was significantly higher in cancerous lesions (IPMN with high-grade dysplasia and IPMN-IC) than in noncancerous lesions (IPMN with low-grade dysplasia and IPMN with intermediate-grade dysplasia), with a sensitivity of 76.1% and a

specificity of 100% ( $P < .001$ ). We also identified a significant difference in IMP3 expression between cancerous lesions and noncancerous lesions in biopsy specimens ( $P = .027$ ). In IPMN-IC, disease-specific survival was significantly shorter in the high-expression group ( $>50\%$  tumor staining) than in the low-expression group ( $\leq 50\%$  tumor staining;  $P = .0069$ ). In conclusion, our findings show that IMP3 is a useful diagnostic marker for distinguishing between noncancerous and cancerous lesions and is a valuable prognostic biomarker in IPMN.

[296]

**TÍTULO / TITLE:** - Clinical and prognostic significance of Yes-associated protein in colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0751-](#)

[X](#)

**AUTORES / AUTHORS:** - Wang Y; Xie C; Li Q; Xu K; Wang E

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, North 2<sup>nd</sup> Road 92, Heping Ward, Shenyang, Liaoning Province, People's Republic of China, [wangyanpaper123@yahoo.com.cn](mailto:wangyanpaper123@yahoo.com.cn).

**RESUMEN / SUMMARY:** - The Hippo signaling pathway is a critical regulator of organ size control during development, and its deregulation is associated with cancers. Acting downstream of this pathway, Yes-associated protein (YAP) was implicated in tumorigenesis. The present study aimed to explore the expression patterns and clinical significance of YAP in human colorectal cancer (CRC). In addition, we investigated the relationship between YAP expression and Wnt/beta-catenin pathway activation in CRC. A total of 139 cases of CRC tissues were investigated by immunohistochemistry for the expression of YAP, cyclin D1, and beta-catenin. The association between YAP expression and clinicopathologic features was analyzed. Our results showed that YAP was overexpressed in 52.5 % (73/139) cases of CRC and predominantly presented in the nucleus. There was an excellent correlation between YAP expression and pTNM stage ( $p = 0.0024$ ). YAP expression in CRC was significantly correlated with nodal status ( $p = 0.0034$ ), tumor status ( $p = 0.0382$ ), and cyclin D1 overexpression ( $p < 0.0001$ ). Importantly, YAP expression was associated with short overall survival ( $p < 0.001$ ). Furthermore, patients with YAP-positive and nuclear beta-catenin-positive profiles had worse overall survival. Univariate and multivariate analyses revealed that YAP expression was an independent prognostic indicator of CRC ( $p = 0.0207$ ). Our results indicated that YAP overexpression contributed to the tumorigenesis and played a pivotal role in the progression in CRC, and the interaction of YAP and Wnt/beta-catenin pathways needs further exploration.

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[297]

**TÍTULO / TITLE:** - A novel histone deacetylase (HDAC) inhibitor MHY219 induces apoptosis via up-regulation of androgen receptor expression in human prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Jun;67(5):407-15. doi: 10.1016/j.biopha.2013.01.006. Epub 2013 Feb 16.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2013.01.006](#)

**AUTORES / AUTHORS:** - Patra N; De U; Kim TH; Lee YJ; Ahn MY; Kim ND; Yoon JH; Choi WS; Moon HR; Lee BM; Kim HS

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Molecular Toxicology, College of Pharmacy, Pusan National University, San 30, Jangjeon-dong, Geumjeung-gu, Busan 609-735, Republic of Korea.

**RESUMEN / SUMMARY:** - Histone deacetylase (HDAC) inhibitors are a new class of anticancer agents that act by inhibiting cancer cell proliferation and inducing apoptosis in various cancer cell lines. To investigate the anticancer effect of a novel histone deacetylase (HDAC) inhibitor MHY219, its efficacy was compared to that of suberoylanilide hydroxamic acid (SAHA) in human prostate cancer cells. The anticancer effects of MHY219 on cell viability, HDAC enzyme activity, cell cycle regulation, apoptosis and other biological assays were performed. MHY219 was shown to enhance the cytotoxicity on DU145 cells (IC<sub>50</sub>, 0.36μM) when compared with LNCaP (IC<sub>50</sub>, 0.97μM) and PC3 cells (IC<sub>50</sub>, 5.12μM). MHY219 showed a potent inhibition of total HDAC activity when compared with SAHA. MHY219 increased histone H3 hyperacetylation and reduced the expression of class I HDACs (1, 2 and 3) in prostate cancer cells. MHY219 effectively increased the sub-G1 fraction of cells through p21 and p27 dependent pathways in DU145 cells. MHY219 significantly induced a G2/M phase arrest in DU145 and PC3 cells and arrested the cell cycle at G0/G1 phase in LNCaP cells. Furthermore, MHY219 effectively increased apoptosis in DU145 and LNCaP cells, but not PC3 cells, according to Annexin V/PI staining and Western blot analysis. These results indicate that MHY219 is a potent HDAC inhibitor that targets regulating multiple aspects of cancer cell death and might have preclinical value in human prostate cancer chemotherapy, warranting further investigation.

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[298]

**TÍTULO / TITLE:** - Palladium(II) saccharinate complexes with bis(2-pyridylmethyl)amine induce cell death by apoptosis in human breast cancer cells in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem. 2013 Jun 1;21(11):3016-21. doi: 10.1016/j.bmc.2013.03.073. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmc.2013.03.073](http://1016/j.bmc.2013.03.073)

**AUTORES / AUTHORS:** - Ari F; Ulukaya E; Sarimahmut M; Yilmaz VT

**INSTITUCIÓN / INSTITUTION:** - Uludag University, Medical School, Department of Clinical Biochemistry, 16059 Bursa, Turkey.

**RESUMEN / SUMMARY:** - The outcomes of breast cancer patients are still poor although new compounds have recently been introduced into the clinic. Therefore, novel chemical approaches are required. In the present study, palladium(II) and corresponding platinum(II) complexes containing bis(2-pyridylmethyl)amine (bpma) and saccharine were synthesized and tested against human breast cancer cell lines, MCF-7 and MDA-MB-231, in vitro. Cytotoxicity was first screened by the MTT assay and the results were further confirmed by the ATP assay. The palladium complexes 1 and 3 yielded stronger cytotoxicity than the corresponding platinum complexes 2 and 4 at the same doses. The palladium complex 3 was found to be the most cytotoxic one. Therefore, a more comprehensive study was carried out with this complex only. The mode of cell death was determined morphologically under fluorescent microscope and biochemically with detection of active caspase-3 and PARP cleavage by Western blot. Changes in apoptosis-related gene expressions were measured with qPCR. It was demonstrated that complex 3 caused cell death by apoptosis determined by fluorescence imaging and Western blot. As a sign of apoptosis, PARP was cleaved in both of the cell lines. In addition, caspase-3 was cleaved in MDA-MB-231 cells while this cleavage was not observed in MCF-7. The results show that the complex 3 is a promising anti-cancer compound against breast cancer with an IC<sub>50</sub> value of 3.9 μM for MCF-7 and 4.2 μM for MDA-MB-231 cells, which warrants further animal experiments.

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[299]

**TÍTULO / TITLE:** - Improvement of the boron neutron capture therapy (BNCT) by the previous administration of the histone deacetylase inhibitor sodium butyrate for the treatment of thyroid carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Radiat Environ Biophys. 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [1007/s00411-013-0470-0](http://1007/s00411-013-0470-0)

**AUTORES / AUTHORS:** - Perona M; Rodriguez C; Carpano M; Thomasz L; Nieves S; Olivera M; Thorp S; Curotto P; Pozzi E; Kahl S; Pisarev M; Juvenal G; Dagrosa A

**INSTITUCIÓN / INSTITUTION:** - Department of Radiobiology, National Atomic Energy Commission (CNEA), Avenida General Paz 1499, San Martin (1650), Buenos Aires, Argentina.

**RESUMEN / SUMMARY:** - We have shown that boron neutron capture therapy (BNCT) could be an alternative for the treatment of poorly differentiated thyroid carcinoma (PDTc). Histone deacetylase inhibitors (HDACi) like sodium butyrate (NaB) cause hyperacetylation of histone proteins and show capacity to increase the gamma irradiation effect. The purpose of these studies was to investigate the use of the NaB as a radiosensitizer of the BNCT for PDTc. Follicular thyroid carcinoma cells (WRO) and rat thyroid epithelial cells (FRTL-5) were incubated with 1 mM NaB and then treated with boronophenylalanine 10BPA (10 µg 10B ml<sup>-1</sup>) + neutrons, or with 2, 4-bis (alpha,beta-dihydroxyethyl)-deutero-porphyrin IX 10BOPP (10 µg 10B ml<sup>-1</sup>) + neutrons, or with a neutron beam alone. The cells were irradiated in the thermal column facility of the RA-3 reactor (flux = (1.0 +/- 0.1) x 10<sup>10</sup> n cm<sup>-2</sup> s<sup>-1</sup>). Cell survival decreased as a function of the physical absorbed dose in both cell lines. Moreover, the addition of NaB decreased cell survival (p < 0.05) in WRO cells incubated with both boron compounds. NaB increased the percentage of necrotic and apoptotic cells in both BNCT groups (p < 0.05). An accumulation of cells in G2/M phase at 24 h was observed for all the irradiated groups and the addition of NaB increased this percentage. Biodistribution studies of BPA (350 mg kg<sup>-1</sup> body weight) 24 h after NaB injection were performed. The in vivo studies showed that NaB treatment increases the amount of boron in the tumor at 2-h post-BPA injection (p < 0.01). We conclude that NaB could be used as a radiosensitizer for the treatment of thyroid carcinoma by BNCT.

[300]

**TÍTULO / TITLE:** - Membranous expression of podocalyxin-like protein is an independent factor of poor prognosis in urothelial bladder cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 May 7. doi: 10.1038/bjc.2013.215.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.215](#)

**AUTORES / AUTHORS:** - Boman K; Larsson AH; Segersten U; Kuteeva E; Johannesson H; Nodin B; Eberhard J; Uhlen M; Malmstrom PU; Jirstrom K

**INSTITUCIÓN / INSTITUTION:** - Division of Pathology, Department of Clinical Sciences, Lund University, Skane University Hospital, 221 85 Lund, Sweden.

**RESUMEN / SUMMARY:** - Background: Membranous expression of the anti-adhesive glycoprotein podocalyxin-like (PODXL) has previously been found to correlate with poor prognosis in several major cancer forms. Here we examined the prognostic impact of PODXL expression in urothelial bladder cancer. Methods: Immunohistochemical PODXL expression was examined in tissue microarrays with tumours from two independent cohorts of patients with urothelial bladder cancer: n=100 (Cohort I) and n=343 (Cohort II). The impact of PODXL expression on disease-specific survival (DSS; Cohort II), 5-year overall survival (OS; both cohorts) and 2-year progression-free survival (PFS; Cohort II) was assessed. Results: Membranous PODXL expression was

significantly associated with more advanced tumour (T) stage and high-grade tumours in both cohorts, and a significantly reduced 5-year OS (unadjusted HR=2.25 in Cohort I and 3.10 in Cohort II, adjusted HR=2.05 in Cohort I and 2.18 in Cohort II) and DSS (unadjusted HR=4.36, adjusted HR=2.70). In patients with Ta and T1 tumours, membranous PODXL expression was an independent predictor of a reduced 2-year PFS (unadjusted HR=6.19, adjusted HR=4.60) and DSS (unadjusted HR=8.34, adjusted HR=7.16). Conclusion: Membranous PODXL expression is an independent risk factor for progressive disease and death in patients with urothelial bladder cancer. British Journal of Cancer advance online publication, 7 May 2013; doi:10.1038/bjc.2013.215 [www.bjcancer.com](http://www.bjcancer.com).

[301]

**TÍTULO / TITLE:** - A Role for Adjuvant RFA in Managing Hepatic Metastases from Gastrointestinal Stromal Tumors (GIST) After Treatment with Targeted Systemic Therapy Using Kinase Inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cardiovasc Intervent Radiol. 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1007/s00270-013-0615-](http://1007/s00270-013-0615-1)

[1](#)

**AUTORES / AUTHORS:** - Hakime A; Le Cesne A; Deschamps F; Farouil G; Boudabous S; Auperin A; Domont J; Debaere T

**INSTITUCIÓN / INSTITUTION:** - Gustave Roussy Institute, 39 r Camille Desmoulins, 94805, Villejuif, France, [thakime@yahoo.com](mailto:thakime@yahoo.com).

**RESUMEN / SUMMARY:** - PURPOSE: This study was designed to assess the role of radiofrequency ablation (RFA) in the multimodality management of gastrointestinal stromal tumors (GIST) in patients undergoing targeted tyrosine kinase inhibitor therapy (TKI) for liver metastases. METHODS: Outcomes of 17 patients who underwent liver RFA for 27 metastatic GIST after TKI therapy, from January 2004 to March 2012, were retrospectively analyzed. Mean maximum tumor diameter was 2.5 +/- 1 cm (range 0.9-4.5 cm). In seven patients (group A), RFA of all residual tumors was performed, with curative intent, and TKI therapy was discontinued. In five patients (group B), RFA of all residual tumors was performed upon achieving the best morphological response with TKI therapy, which was maintained after RFA. In another five patients (group C), RFA was performed on individual liver metastases which were progressive under TKI therapy. RESULTS: All 27 targeted tumors were completely ablated, without local recurrence during the mean follow-up period of 49 months. No major complications occurred. Two minor complications were reported (11 %). Only two patients (both in group C) died at 20 and 48 months. Two-year progression-free survival (PFS) after RFA was 29 % in group A, 75 % in group B, and 20 % in group C. CONCLUSIONS: RFA in patients, previously treated with TKI, is feasible and safe. Our data suggest that RFA is a useful

therapeutic option in patients with metastatic GIST and should be performed at the time of best clinical response with patient maintained under TKI after the procedure.

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[302]

**TÍTULO / TITLE:** - A phase II study of the oral VEGF receptor tyrosine kinase inhibitor vatalanib (PTK787/ZK222584) in myelodysplastic syndrome: Cancer and Leukemia Group B study 10105 (Alliance).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Invest New Drugs. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1007/s10637-013-9978-](#)

[Z](#)

**AUTORES / AUTHORS:** - Gupta P; Mulkey F; Hasserjian RP; Sanford BL; Vij R; Hurd DD; Odenike OM; Bloomfield CD; Owzar K; Stone RM; Larson RA

**INSTITUCIÓN / INSTITUTION:** - University of Minnesota, Minneapolis, MN, USA, [gupta013@umn.edu](mailto:gupta013@umn.edu).

**RESUMEN / SUMMARY:** - Background: Angiogenesis is implicated in the pathophysiology and progression of myelodysplastic syndromes (MDS). Vatalanib (PTK787/ZK222584; Novartis and Schering AG) inhibits receptor tyrosine kinases of vascular endothelial growth factor, platelet derived growth factor and c-Kit. We examined whether vatalanib induces hematological responses in MDS and/or delays progression to acute myeloid leukemia (AML) or death. Methods: Two cohorts were studied. Vatalanib 1250 mg orally was given once daily (cohort 1) or 750-1250 mg once daily in an intra-patient dose escalating schedule (cohort 2) in 28-day cycles to 155 patients with MDS; 142 patients were evaluable for response and 153 for toxicity. Results: The median age was 70.5 years; 51 % had low risk (International Prognostic Scoring System {IPSS} Low/Intermediate-1) and 32 % had high risk (IPSS Intermediate-2/High) MDS. Hematological improvement was achieved in 7/142 (5 %) patients; all 7 were among the 47 patients able to remain on vatalanib for at least 3 months (hematological improvement achieved in 15 % of these 47 patients). For patients with low risk and high risk MDS, respectively, median progression-free survivals were 15 and 6 months, median times to transformation to AML were 28 and 6 months, and median overall survivals were 36 and 10 months. The most frequent non-hematological adverse events grade  $\geq 2$  were fatigue, nausea or vomiting, dizziness, anorexia, ataxia, diarrhea, and pain. Two deaths (one intra-cerebral hemorrhage and one sudden death) were possibly related to vatalanib. Conclusions: Vatalanib induces improvement in blood counts in a small proportion of MDS patients. Clinical applicability is limited by side effects.

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[303]

**TÍTULO / TITLE:** - LukS-PV induces mitochondrial-mediated apoptosis and G/G cell cycle arrest in human acute myeloid leukemia THP-1 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biochem Cell Biol. 2013 May 20. pii: S1357-2725(13)00148-9. doi: 10.1016/j.biocel.2013.05.011.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biocel.2013.05.011](#)

**AUTORES / AUTHORS:** - Bu S; Xie Q; Chang W; Huo X; Chen F; Ma X

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, Anhui Provincial Hospital, Anhui Medical University, Hefei 230001, PR China.

**RESUMEN / SUMMARY:** - The S component (LukS-PV) is one of the two components of Panton-Valentine leukocidin (PVL), which is a pore-forming cytotoxin secreted by *Staphylococcus aureus*, with the ability to lyse leukocytes. In this study, LukS-PV had the ability to induce apoptosis in the human acute myeloid leukemia (AML) cell line THP-1. Therefore, we investigated the mechanisms of LukS-PV-induced apoptosis in THP-1 cells. THP-1 cells treated with LukS-PV, resulted in a significant inhibition of proliferation in a dose- and time-dependent manner, and induced G0/G1 arrest associated with an inhibition of cell cycle arrest regulatory protein (cyclin D1) in a dose- and time-dependent manner, as measured by flow cytometry (FCM). After 12h exposure to LukS-PV (1.00µM), annexin V-EGFP/propidium iodide (PI) FCM revealed that 19.5+/-3.6% of THP-1 cells were apoptotic, and terminal deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) staining also revealed THP-1 cells were apoptotic. Chip analysis of 84 apoptosis-related genes demonstrated that 9 genes were up-regulated at least 2-fold and that 5 genes were down-regulated at least 2-fold in the treatment group when compared with levels in the control group. Western blotting revealed that the expression of caspase-8 increased significantly (approximately 4-fold). The levels of caspase-9, -3 and Bax increased significantly, and levels of Bcl-2 decreased rapidly with LukS-PV treatment. These data suggest that LukS-PV acts as an anti-leukemia agent and activates AML cell apoptosis via the mitochondrial pathway. Therefore, LukS-PV may be a multi-targeting drug candidate for the prevention and therapy of AML.

[304]

**TÍTULO / TITLE:** - Oncostatin-M promotes phenotypic changes associated with mesenchymal and stem cell-like differentiation in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncogene. 2013 Apr 15. doi: 10.1038/onc.2013.105.

●●Enlace al texto completo (gratis o de pago) [1038/onc.2013.105](#)

**AUTORES / AUTHORS:** - West NR; Murray JI; Watson PH

**INSTITUCIÓN / INSTITUTION:** - 1] Deeley Research Centre, British Columbia Cancer Agency, Victoria, British Columbia, Canada [2] Department of

Biochemistry and Microbiology, University of Victoria, Victoria, British Columbia, Canada.

**RESUMEN / SUMMARY:** - Cancer stem cell (CSC) biology and the epithelial-to-mesenchymal transition (EMT) are thought to be mechanistically linked and may be key components of cancer development and progression. However, stimuli that induce EMT and CSC-like features ('stemness') are poorly defined. We and others have shown that the inflammatory cytokine oncostatin-M (OSM) mediates phenotypic changes in breast cancer that are consistent with EMT and dedifferentiation, including enhanced migration and loss of hormone receptors. In this study, we have expanded on these prior observations to determine whether OSM is a cell-extrinsic driver of EMT and/or stemness. OSM stimulation of the luminal breast cancer cell lines MCF7 and T47D induced EMT features including loss of membranous E-cadherin and induction of snail and slug expression. OSM treatment markedly enhanced the formation of mammospheres (up to 20-fold,  $P < 0.001$ ), which displayed high expression of the pluripotency factor SOX2. The proportion of cells with a CD44<sup>high</sup>CD24<sup>-/low</sup> phenotype was similarly increased by OSM ( $P < 0.001$ ). OSM-induced mammosphere formation and CD44<sup>high</sup>CD24<sup>-/low</sup> induction was dependent on PI3K signalling. In silico analysis of human breast tumours (from a publicly available data set,  $n=322$ ) confirmed that co-expression of a PI3K transcriptional signature, but not MAPK or STAT3 signatures, was necessary to detect an association between OSMR and poor prognosis. Assessment of a second in silico data set ( $n=241$  breast tumours) confirmed a significant relationship between OSMR, markers of EMT and CSCs, and chemotherapy resistance. Direct analysis of mRNA expression by RT-PCR in a third cohort ( $n=72$  breast tumours) demonstrated that high expression of OSM is associated positively with indicators of EMT (SNAI1,  $P < 0.001$ ) and stemness (SOX2,  $P < 0.05$ ). Our data suggest for the first time that OSM may promote a clinically relevant EMT/CSC-like phenotype in human breast cancer via a PI3K-dependent mechanism. Oncogene advance online publication, 15 April 2013; doi:10.1038/onc.2013.105.

[305]

**TÍTULO / TITLE:** - Expression of steroid receptor coactivator 3 in ovarian epithelial cancer is a poor prognostic factor and a marker for platinum resistance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 May 28;108(10):2039-44. doi: 10.1038/bjc.2013.199. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.199](#)

**AUTORES / AUTHORS:** - Palmieri C; Gojis O; Rudraraju B; Stamp-Vincent C; Wilson D; Langdon S; Gourley C; Faratian D

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Molecular and Clinical Cancer Medicine, Institute of translational Medicine, University of Liverpool, Liverpool, UK [2] Cancer Research UK Laboratories, Division of Cancer, Imperial College London, Du Cane Road, London, UK.

**RESUMEN / SUMMARY:** - Background: Steroid receptor coactivator 3 (SRC3) is an important coactivator of a number of transcription factors and is associated with a poor outcome in numerous tumours. Steroid receptor coactivator 3 is amplified in 25% of epithelial ovarian cancers (EOCs) and its expression is higher in EOCs compared with non-malignant tissue. No data is currently available with regard to the expression of SRC-3 in EOC and its influence on outcome or the efficacy of treatment. Methods: Immunohistochemistry was performed for SRC3, oestrogen receptor-alpha, HER2, PAX2 and PAR6, and protein expression was quantified using automated quantitative immunofluorescence (AQUA) in 471 EOCs treated between 1991 and 2006 with cytoreductive surgery followed by first-line treatment platinum-based therapy, with or without a taxane. Results: Steroid receptor coactivator 3 expression was significantly associated with advanced stage and was an independent prognostic marker. High expression of SRC3 identified patients who have a significantly poorer survival with single-agent carboplatin chemotherapy, while with carboplatin/paclitaxel treatment such a difference was not seen. Conclusion: Steroid receptor coactivator 3 is a poor prognostic factor in EOCs and appears to identify a population of patients who would benefit from the addition of taxanes to their chemotherapy regimen, due to intrinsic resistance to platinum therapy.

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[306]

**TÍTULO / TITLE:** - CD13 expression is an independent adverse prognostic factor in adults with Philadelphia chromosome negative B cell acute lymphoblastic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 Jul;37(7):759-64. doi: 10.1016/j.leukres.2013.04.006. Epub 2013 May 1.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.04.006](http://1016/j.leukres.2013.04.006)

**AUTORES / AUTHORS:** - Craddock KJ; Chen Y; Brandwein JM; Chang H

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Pathology, University Health Network, Toronto, ON, Canada.

**RESUMEN / SUMMARY:** - In adults with precursor-B lymphoblastic leukemia (BCP-ALL) there remain a majority of patients who fall in an intermediate cytogenetics risk category with a heterogeneous outcome. We analyzed immunophenotypic and cytogenetic factors retrospectively in 126 consecutive adults with BCR-ABL negative BCP-ALL who were treated with a pediatric-based protocol at a single institution over a 10 year period. In addition to age,

WBC and cytogenetic findings, CD13 positivity was an independent poor prognostic indicator for overall survival (OS,  $p=0.049$ ), event-free survival (EFS,  $p=0.013$ ), and relapse-free survival (RFS,  $p<0.001$ ). The prognostic value of CD13 was primarily seen in patients with normal or intermediate risk cytogenetics. A risk model that includes age $>60$  years, WBC $>30 \times 10^9/L$ , SWOG high/very high risk cytogenetics and CD13 positivity, performs better than a risk model of cytogenetics alone for stratifying patients by OS ( $p=0.001$ ), EFS ( $p=7 \times 10^{-4}$ ) and RFS ( $p=8 \times 10^{-4}$ ). Incorporating CD13 into a scoring system provides high discrimination for relapse risk and survival.

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[307]

**TÍTULO / TITLE:** - Prognostic and predictive value of estrogen receptor 1 expression in completely resected non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Apr 12. doi: 10.1002/ijc.28209.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28209](#)

**AUTORES / AUTHORS:** - Brueckl WM; Al-Batran SE; Ficker JH; Claas S; Atmaca A; Hartmann A; Rieker RJ; Wirtz RM

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, 3, Klinikum Nurnberg, Nuremberg, Germany; Comprehensive Cancer Center (CCC) Erlangen-Nuremberg, Erlangen, Germany; Paracelsus Medical University Nuremberg, Nuremberg, Germany.

**RESUMEN / SUMMARY:** - Adjuvant chemotherapy (ACT) leads to a modest improvement in survival among patients with completely resected non-small cell lung cancer (NSCLC) but molecular predictors are still rare. Publicly available gene microarray, clinical and follow-up data from two different studies on early-stage NSCLC were used to determine the expression of estrogen receptor 1 (ESR1). Expression values were calculated against clinical and survival data in a training set ( $n = 138$ ) and a test set (subpopulation from the adjuvant JBR.10 study) allowing the determination of the prognostic effect of ESR1 in the observational arm as well as the predictive effect of ESR1 regarding ACT. Data were well balanced in terms of ESR1 expression. ESR1 high expression was of significant positive prognostic value in the training set and this could be confirmed in the test set cohort (hazard ratio for overall survival 0.248, 95% confidence interval: 0.088-0.701;  $p = 0.008$ ). Additionally, ESR1 low tumors showed a benefit from ACT in terms of 5-year survival (33.3% observation arm and 77.8% ACT arm;  $p = 0.003$ ), whereas patients with ESR1 high tumors did not have any benefit from ACT (test of interaction  $p = 0.024$ ). ESR1 is an independent positive prognostic factor for survival in early-stage NSCLC patients. Patients with ESR1 high tumors did not benefit from ACT.

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[308]

**TÍTULO / TITLE:** - Concurrent expression of C4.4A and Tenascin-C in tumor cells relates to poor prognosis of esophageal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 May 24. doi: 10.3892/ijo.2013.1956.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1956](#)

**AUTORES / AUTHORS:** - Ohtsuka M; Yamamoto H; Oshiro R; Takahashi H; Masuzawa T; Uemura M; Haraguchi N; Nishimura J; Hata T; Yamasaki M; Takemasa I; Miyata H; Mizushima T; Takiguchi S; Doki Y; Mori M

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterological Surgery, Graduated School of Medicine, Osaka University, Osaka 565-0871, Japan.

**RESUMEN / SUMMARY:** - C4.4A is a glycolipid-anchored membrane protein expressed in several human malignancies. We recently found that C4.4A expression was associated with poor prognosis of esophageal squamous carcinoma cells (ESCCs), but the underlying mechanism is unknown. To uncover this, we performed PCR array analysis using the HCT116 cell line, a positive control for C4.4A expression and we found that Tenascin-C (TNC) among the many adhesion molecules and extracellular matrix proteins was the best candidate for C4.4A molecule induction. Based on in vitro studies using the TE8 esophageal cancer cells, we examined by immunohistochemistry TNC expression in 111 ESCCs. We found that the TNC-positive group (24.3%) had significantly poorer prognosis than the TNC-negative group in 5-year overall survival. We also found there was a significant correlation between TNC and C4.4A in ESCC tissues (P=0.007). Finally, we found that only the double-positive group for C4.4A and TNC had a significantly worse prognosis (P=0.005). Our data suggest that TNC expression in ESCC may in part explain why C4.4A is associated with a poor prognosis of ESCC since TNC can promote invasion and metastasis.

[309]

**TÍTULO / TITLE:** - Pharmacological inhibition of polycomb repressive complex-2 activity induces apoptosis in human colon cancer stem cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Cell Res. 2013 Jun 10;319(10):1463-70. doi: 10.1016/j.yexcr.2013.04.006. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago)

[1016/j.yexcr.2013.04.006](#)

**AUTORES / AUTHORS:** - Benoit YD; Witherspoon MS; Laursen KB; Guezguez A; Beausejour M; Beaulieu JF; Lipkin SM; Gudas LJ

**INSTITUCIÓN / INSTITUTION:** - Pharmacology Department, Weill Cornell Medical College, NY 10065, USA. Electronic address: [yannick.benoit@usherbrooke.ca](mailto:yannick.benoit@usherbrooke.ca).

**RESUMEN / SUMMARY:** - Colorectal cancer is among the leading causes of cancer death in the USA. The polycomb repressive complex 2 (PRC2), including core components SUZ12 and EZH2, represents a key epigenetic

regulator of digestive epithelial cell physiology and was previously shown to promote deleterious effects in a number of human cancers, including colon. Using colon cancer stem cells (CCSC) isolated from human primary colorectal tumors, we demonstrate that SUZ12 knockdown and treatment with DZNep, one of the most potent EZH2 inhibitors, increase apoptosis levels, marked by decreased Akt phosphorylation, in CCSCs, while embryonic stem (ES) cell survival is not affected. Moreover, DZNep treatments lead to increased PTEN expression in these highly tumorigenic cells. Taken together, our findings suggest that pharmacological inhibition of PRC2 histone methyltransferase activity may constitute a new, epigenetic therapeutic strategy to target highly tumorigenic and metastatic colon cancer stem cells.

[310]

**TÍTULO / TITLE:** - Retraction Note: Oleandrin-Mediated Expression of Fas Potentiates Apoptosis in Tumor Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Immunol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1007/s10875-013-9884-](#)

[3](#)

**AUTORES / AUTHORS:** - Sreenivasan Y; Raghavendra PB; Manna SK

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Immunology, Centre for DNA Fingerprinting & Diagnostics (CDFD), ECIL Road, Nacharam, Hyderabad, 500076, India.

[311]

**TÍTULO / TITLE:** - Tumor necrosis factor alpha induced warburg-like metabolism and is reversed by anti-inflammatory curcumin in breast epithelial cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 May 10. doi: 10.1002/ijc.28264.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28264](#)

**AUTORES / AUTHORS:** - Vaughan RA; Garcia-Smith R; Dorsey J; Griffith JK; Bisoffi M; Trujillo KA

**INSTITUCIÓN / INSTITUTION:** - Department of Health, Exercise and Sports Science, University of New Mexico, Albuquerque, NM 87131; Department of Biochemistry and Molecular Biology, University of New Mexico Health Sciences Center, Albuquerque, NM 87131; Department of Individual, Family and Community Education: Nutrition, University of New Mexico, Albuquerque, NM 87131.

**RESUMEN / SUMMARY:** - The re-programming of cellular metabolism in cancer cells is a well-documented effect. It has previously been shown that common oncogene expression can induce aerobic glycolysis in cancer cells. However, the direct effect of an inflammatory microenvironment on cancer cell metabolism

is not known. Here, we illustrate that treatment of non-malignant (MCF-10a) and malignant (MCF-7) breast epithelial cells with low-level (10 ng/ml) Tumor Necrosis Factor alpha (TNF-alpha) significantly increased glycolytic reliance, lactate export, and expression of the glucose transporter, GLUT1. TNF-alpha decreased total mitochondrial content, however oxygen consumption rate was not significantly altered, meaning that overall mitochondrial function was increased. Upon glucose starvation, MCF7 cells treated with TNF-alpha, demonstrated significantly lower viability than non-treated cells. Interestingly, these properties can be partially reversed by co-incubation with the anti-inflammatory agent curcumin in a dose-dependent manner. This work demonstrates that aerobic glycolysis can be directly induced by an inflammatory microenvironment independent of additional genetic mutations and signals from adjacent cells. Furthermore, we have identified that a natural dietary compound can reverse this effect. © 2013 Wiley Periodicals, Inc.

[312]

**TÍTULO / TITLE:** - Safety and efficacy of adjuvant pegylated interferon therapy for metastatic tumor antigen 1-positive hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer. 2013 Jun 15;119(12):2239-46. doi: 10.1002/cncr.28082. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [1002/cncr.28082](#)

**AUTORES / AUTHORS:** - Lee D; Chung YH; Kim JA; Park WH; Jin YJ; Shim JH; Ryu SH; Jang MK; Yu E; Lee YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Metastatic tumor antigen 1 (MTA1) overexpression is closely associated with postoperative recurrence of hepatocellular carcinoma (HCC). It has been suggested that pegylated interferon (Peg-IFN) can prevent the occurrence of HCC in patients who have chronic viral hepatitis. In this study, the authors examined whether postoperative adjuvant Peg-IFN therapy can reduce the recurrence of MTA1-positive HCC after curative surgical resection. METHODS: In this case-control study, 93 patients with MTA1-positive HCC who underwent curative surgical resection were prospectively enrolled. The median patient age was 53 years (range, 27-78); there were 65 men and 28 women; the etiology was hepatitis B virus (HBV) in 77 patients, hepatitis C virus (HCV) in 6 patients, and non-HBV/non-HCV in 10 patients; 31 patients received Peg-IFN (Peg-INTRON®) subcutaneously at a dose of 50 mug per week for 12 months (the Peg-IFN group); and the remaining 62 patients were followed only and did not receive any adjuvant therapies (control group). Patients were followed every 1 to 3 months for a median of 24 months. RESULTS: HCC recurred postoperatively in 26 of 93 patients (28%), and 9 patients (10%) died during follow-up. The overall

cumulative recurrence rates were significantly lower in the Peg-IFN group than in the control group (7% and 14% vs 24% and 34% at 1 year and 2 years, respectively;  $P < .05$ ). In addition, the 1-year and 2-year cumulative survival rates were higher in the Peg-IFN group compared with the control group (100% vs 93% and 100% vs 87%, respectively;  $P < .05$ ). In multivariate analysis, the receipt of adjuvant Peg-IFN therapy, in addition to having a lower Cancer of the Liver Italian Program score and being a woman, was an independent, favorable factor for a lower risk of postoperative recurrence. CONCLUSIONS: The current data indicate that adjuvant Peg-IFN therapy may reduce the recurrence of HCC in patients who have MTA1-positive HCC after curative surgical resection. Cancer 2013;119:2239-2246. © 2013 American Cancer Society.

[313]

**TÍTULO / TITLE:** - An HDAC inhibitor enhances cancer therapeutic efficiency of RNA polymerase III promoter-driven IDO shRNA.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Gene Ther. 2013 May 17. doi: 10.1038/cgt.2013.27.

●●Enlace al texto completo (gratis o de pago) [1038/cgt.2013.27](#)

**AUTORES / AUTHORS:** - Yen MC; Weng TY; Chen YL; Lin CC; Chen CY; Wang CY; Chao HL; Chen CS; Lai MD

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Biochemistry and Molecular Biology, College of Medicine, National Cheng Kung University, Tainan, Taiwan [2] Infectious diseases and Signaling Research Center, National Cheng Kung University, Tainan, Taiwan.

**RESUMEN / SUMMARY:** - Histone deacetylase (HDAC) inhibitors are used in treating certain human malignancies. Our laboratories demonstrated their capability in enhancing antitumor effect of DNA vaccine driven by an RNA polymerase II (RNA pol II) promoter. However, it is unknown whether HDAC inhibitors enhance the therapeutic short hairpin RNA (shRNA) expressed by an RNA polymerase III (RNA pol III) promoter. We investigated whether HDAC inhibitors augmented antitumor effect of indoleamine 2,3 dioxygenase (IDO) shRNA. HDAC inhibitor OSU-HDAC42 and suberoylanilide hydroxamic acid enhanced RNA pol III-driven U6 and H1 promoter activity in three different cell types in vitro: 293, NIH3T3 and dendritic cell line DC2.4. Subcutaneous injection of OSU-HDAC42 enhanced U6 and H1 promoter activity on abdominal skin of mice in vivo. Combination of IDO shRNA and OSU-HDAC42 increased antitumor effect of IDO shRNA in MBT-2 murine bladder tumor model. IDO shRNA induced tumor-infiltrating CD8+ and CD4+ T cells, whereas OSU-HDAC42 treatment induced tumor-infiltrating CD4+ T cells. Combination of OSU-HDAC42 and IDO shRNA further induced tumor-infiltrating natural killer cells and enhanced interferon-gamma in lymphocytes, but suppressed interleukin (IL)-4 expression of lymphocytes. In addition, OSU-HDAC42

treatment did not alter mRNA expression of IL-12 and tumor necrosis factor-alpha. In conclusion, HDAC inhibitor OSU-HDAC42 may serve as adjuvant of the therapeutic shRNA expressed by an RNA pol III promoter. Cancer Gene Therapy advance online publication, 17 May 2013; doi:10.1038/cgt.2013.27.

[314]

**TÍTULO / TITLE:** - Combination of 18F-FDG PET/CT and Diffusion-Weighted MR Imaging as a Predictor of Histologic Response to Neoadjuvant Chemotherapy: Preliminary Results in Osteosarcoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Nucl Med. 2013 May 13.

●●Enlace al texto completo (gratis o de pago)

[2967/jnumed.112.115964](#)

**AUTORES / AUTHORS:** - Byun BH; Kong CB; Lim I; Choi CW; Song WS; Cho WH; Jeon DG; Koh JS; Lee SY; Lim SM

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences (KIRAMS), Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - We evaluated the potential of 18F-FDG PET/CT and diffusion-weighted imaging (DWI) to monitor the histologic response in patients with extremity osteosarcoma receiving neoadjuvant chemotherapy, using sequential PET/CT and MR imaging. **METHODS:** We prospectively registered 28 patients with high-grade osteosarcoma treated with 2 cycles of neoadjuvant chemotherapy and surgery. All patients underwent sequential 18F-FDG PET/CT and MR imaging before (PET/MR1) and after neoadjuvant chemotherapy (PET/MR2). Maximum standardized uptake value (SUV), tumor volume based on MR imaging (MRV), and the mean apparent diffusion coefficient (ADC) values were measured on PET/MR1 (SUV1, MRV1, and ADC1) and PET/MR2 (SUV2, MRV2, and ADC2). The percentage changes in maximum SUV (SUV), MRV (MRV), and ADC (ADC) were calculated, and the correlations among these parameters were evaluated. After surgery, the effects of neoadjuvant chemotherapy were graded histopathologically: grades III and IV (necrosis of  $\geq 90\%$ ) indicated a good response, and grades I and II (necrosis of  $< 90\%$ ) indicated a poor response. The optimum cutoff values of SUV, MRV, ADC, and their combination for predicting histologic response were assessed by single- and multi-receiver-operating-characteristic curve analysis. **RESULTS:** Twenty-seven patients were enrolled in the present study after 1 patient with inadequate acquisition of MR imaging was excluded. SUV and ADC negatively correlated with each other ( $\rho = -0.593$ ,  $P = 0.001$ ), and MRV did not correlate with SUV or ADC. The cutoff value, sensitivity, specificity, and accuracy for predicting good histologic response were  $\leq -52\%$ , 67%, 87%, and 78%, respectively, for SUV and  $> 13\%$ , 83%, 73%, and 78%, respectively, for ADC. However, MRV did not predict histologic response. Sensitivity, specificity, and accuracy were

83%, 87%, and 85%, respectively, using the combined criterion of SUV  $\leq$  - 31% and ADC  $>$  13%. CONCLUSION: In the current preliminary study, both PET/CT and DWI are useful for predicting histologic response after neoadjuvant chemotherapy in osteosarcoma. Combining PET/CT and DWI may be an effective method to predict the histologic response of patients to neoadjuvant chemotherapy.

[315]

**TÍTULO / TITLE:** - Regulation of cell cycle transition and induction of apoptosis in HL-60 leukemia cells by the combination of *Coriolus versicolor* and *Ganoderma lucidum*.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Jul;32(1):251-7. doi: 10.3892/ijmm.2013.1378. Epub 2013 May 10.

●●Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1378](#)

**AUTORES / AUTHORS:** - Hsieh TC; Wu JM

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, NY 10595, USA.

**RESUMEN / SUMMARY:** - Medicinal mushrooms have served as the mainstay of treatment for a variety of human illnesses in Asian countries, mostly as supplements by cancer patients. Extracts prepared from *Trametes versicolor* under the trade name of I'm-Yunity exhibit anti-tumorigenic activities, as supported by inhibition of the proliferation and induction of apoptosis in malignant cells. Similar effects have also been observed for the Reishi mushroom *Ganoderma lucidum*. The two mushrooms exert their medicinal activities primarily through a family of polysaccharo-peptides. Despite the common identity in their bioactive ingredients, whether their combination might elicit an expanded efficacy and mechanism has not been investigated. In the present study, we investigated similarities and differences between extracts prepared from I'm-Yunity and from a formulation denoted I'm-Yunity-Too combining I'm-Yunity and *Ganoderma lucidum*. By assaying their anti-proliferative and anti-apoptotic effects using human promyelocytic HL-60 cells, we found that the ethanolic extract of I'm-Yunity-Too was more active in inducing cell death compared to I'm-Yunity, based on measured changes in the expression of caspase 3 and Bax. Moreover, ethanolic extracts of I'm-Yunity-Too exhibited more potent activity compared to its aqueous extracts with regard to suppression of the growth and induction of apoptosis, as assayed by the more pronounced downregulation of phosphorylation of Rb and increased cleavage of poly(ADPribose) polymerase (PARP) from its native 112-kDa form to the inactive 89-kDa product. These results suggested that the chemopreventive potential of I'm-Yunity may be enhanced by adding *Ganoderma lucidum* and that their bioactive ingredients potentially exhibit mechanistic synergism suggesting a more efficacious adjunct in chemotherapy.

[316]

**TÍTULO / TITLE:** - CARMA3 overexpression accelerates cell proliferation and inhibits paclitaxel-induced apoptosis through NF-kappaB regulation in breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 25.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0869-](#)

[X](#)

**AUTORES / AUTHORS:** - Zhao T; Miao Z; Wang Z; Xu Y; Wu J; Liu X; You Y; Li J

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology and General Surgery, First Affiliated Hospital, China Medical University, 155 North Nanjing Street, Heping District, Shenyang City, 110001, China.

**RESUMEN / SUMMARY:** - CARMA3 was recently reported to be overexpressed in several cancers and associated with malignant behavior of cancer cells. However, the expression pattern and biological roles of CARMA3 in breast cancer have not been reported. In the present study, we found that CARMA3 was overexpressed in 41.9 % of breast cancer specimens. Significant association was observed between CARMA3 overexpression and TNM stage ( $p = 0.0223$ ), tumor size ( $p = 0.0227$ ), and ErbB-2 status ( $p = 0.0049$ ). Furthermore, knockdown of CARMA3 expression in MDA-MB-435 cells with high endogenous expression decreased cell proliferation and sensitized cell to paclitaxel-induced apoptosis, while overexpression of CARMA3 in MDA-MB-231 cell line promoted cell proliferation and inhibited apoptosis. Further analysis showed that CARMA3 depletion downregulated, and its overexpression upregulated cyclin D1, Bcl-2, and p-IkappaB levels. In conclusion, our study demonstrated that CARMA3 is overexpressed in breast cancers. CARMA3 facilitates proliferation and inhibits apoptosis through nuclear factor-kappaB signaling.

[317]

**TÍTULO / TITLE:** - Low-dose 1,25-dihydroxyvitamin D3 combined with arsenic trioxide synergistically inhibits proliferation of acute myeloid leukemia cells by promoting apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):485-91. doi: 10.3892/or.2013.2444. Epub 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2444](#)

**AUTORES / AUTHORS:** - Bae JY; Kim JW; Kim I

**INSTITUCIÓN / INSTITUTION:** - Cancer Research Institute, Seoul National University, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - Arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) has shown substantial efficacy in the treatment of patients with acute promyelocytic leukemia, a specific subtype of acute myeloid leukemia (AML). However, since not all patients can achieve remission after treatment, it is necessary to develop a novel method to overcome this problem. We investigated the anti-leukemic effect of low-dose 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) in combination with As<sub>2</sub>O<sub>3</sub> on the human AML cell lines HL-60 and K562. The cell viability was in reverse proportion to As<sub>2</sub>O<sub>3</sub> or 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration. In both HL-60 and K562 cells, after the combination treatment with As<sub>2</sub>O<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub> at a 10:1 ratio, the combination index (CI) values were <1 in all treatment groups. In the RT-PCR and western blot analysis, the combination treatment decreased Bcl-2 expression and increased Bax and caspase-3 expression more prominently than the single treatment. In the flow cytometric analysis performed in HL-60 cells, the proportion of late apoptotic cells was 4.9% in the control, 30.0% in cells treated with 1.0 microM As<sub>2</sub>O<sub>3</sub>, 8.1% in cells treated with 100 nM 1,25(OH)<sub>2</sub>D<sub>3</sub>, and 64.3% in cells treated with 1.0 microM As<sub>2</sub>O<sub>3</sub> plus 100 nM 1,25(OH)<sub>2</sub>D<sub>3</sub>. In conclusion, low-dose 1,25(OH)<sub>2</sub>D<sub>3</sub> combined with As<sub>2</sub>O<sub>3</sub> synergistically inhibited proliferation of HL-60 and K562 cells. In addition, this combination activated the apoptosis pathway more prominently than the singledrug treatment.

[318]

**TÍTULO / TITLE:** - Fatigue and weight loss predict survival on circadian chemotherapy for metastatic colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer. 2013 Apr 30. doi: 10.1002/cncr.28072.

●●Enlace al texto completo (gratis o de pago) [1002/cncr.28072](http://1002/cncr.28072)

**AUTORES / AUTHORS:** - Innominato PF; Giacchetti S; Moreau T; Bjarnason GA; Smaaland R; Focan C; Garufi C; Iacobelli S; Tampellini M; Tumolo S; Carvalho C; Karaboue A; Poncet A; Spiegel D; Levi F

**INSTITUCIÓN / INSTITUTION:** - National Institute for Health and Medical Research (INSERM) Unit 776, "Biological Rhythms and Cancers," Villejuif, France; Medical Research Unit (UMR) S0776, Paris South University, Orsay, France; Chronotherapy Unit, Department of Oncology, Public Hospital System of Paris (APHP), Paul Brousse Hospital, Villejuif, France; Faculty of Medicine, Paris South University, le Kremlin-Bicetre, France.

**RESUMEN / SUMMARY:** - BACKGROUND: Chemotherapy-induced neutropenia has been associated with prolonged survival selectively in patients on a conventional schedule (combined 5-fluorouracil, leucovorin, and oxaliplatin [FOLFOX2]) but not on a chronomodulated schedule of the same drugs administered at specific circadian times (chronoFLO4). The authors hypothesized that the early occurrence of chemotherapy-induced symptoms correlated with circadian disruption would selectively hinder the efficacy of

chronotherapy. METHODS: Fatigue and weight loss (FWL) were considered to be associated with circadian disruption based on previous data. Patients with metastatic colorectal cancer (n = 543) from an international phase 3 trial comparing FOLFOX2 with chronoFLO4 were categorized into 4 subgroups according to the occurrence of FWL or other clinically relevant toxicities during the initial 2 courses of chemotherapy. Multivariate Cox models were used to assess the role of toxicity on the time to progression (TTP) and overall survival (OS). RESULTS: The proportions of patients in the 4 subgroups were comparable in both treatment arms (P = .77). No toxicity was associated with TTP or OS on FOLFOX2. The median OS on FOLFOX2 ranged from 16.4 (95% confidence limits [CL], 7.2-25.6 months) to 19.8 months (95% CL, 17.7-22.0 months) according to toxicity subgroup (P = .45). Conversely, FWL, but no other toxicity, independently predicted for significantly shorter TTP (P < .0001) and OS (P = .001) on chronoFLO4. The median OS on chronoFLO4 was 13.8 months (95% CL, 10.4-17.2 months) or 21.1 months (95% CL, 19.0-23.1 months) according to presence or absence of chemotherapy-induced FWL, respectively. CONCLUSIONS: Early onset chemotherapy-induced FWL was an independent predictor of poor TTP and OS only on chronotherapy. Dynamic monitoring to detect early chemotherapy-induced circadian disruption could allow the optimization of rapid chronotherapy and concomitant improvements in safety and efficacy. Cancer 2013. Esta es una cita bibliográfica que va por delante de la publicación en papel. La fecha indicada en la cita provista, NO corresponde con la fecha o la cita bibliográfica de la publicación en papel. La cita bibliográfica definitiva (con el volumen y su paginación) saldrá en 1 ó 2 meses a partir de la fecha de la emisión electrónica-online. \*\*\* This is a bibliographic record ahead of the paper publication. The given date in the bibliographic record does not correspond to the date or the bibliographic citation on the paper publication. The publisher will provide the final bibliographic citation (with the volume, and pagination) within 1 or 2 months from the date the record was published online. © 2013 American Cancer Society.

[319]

**TÍTULO / TITLE:** - A novel serum protein signature associated with resistance to epidermal growth factor receptor tyrosine kinase inhibitors in head and neck squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Apr 9. pii: S0959-8049(13)00213-X. doi: 10.1016/j.ejca.2013.03.011.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.03.011](http://1016/j.ejca.2013.03.011)

**AUTORES / AUTHORS:** - Box C; Mendiola M; Gowan S; Box GM; Valenti M; Brandon AD; Al-Lazikani B; Rogers SJ; Wilkins A; Harrington KJ; Eccles SA

**INSTITUCIÓN / INSTITUTION:** - Tumour Biology & Metastasis Team, Division of Cancer Therapeutics, The Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK.

**RESUMEN / SUMMARY:** - BACKGROUND: Acquired resistance to tyrosine kinase inhibitors (TKIs) is becoming a major challenge in the treatment of many cancers. Epidermal growth factor receptor (EGFR) is overexpressed in squamous carcinomas, notably those of the head and neck (HNSCC), and can be targeted with several TKIs. We aimed to identify soluble proteins suitable for development as markers of EGFR TKI resistance in cancer patients to aid in early and minimally invasive assessment of therapeutic responses. METHODS: Resistant HNSCC cell lines were generated by exposure to an EGFR TKI, gefitinib, in vitro. Cell lines were characterised for their biological behaviour in vitro (using growth inhibition assays, flow cytometry, western blots, antibody arrays and/or immunoassays) and in vivo (using subcutaneous tumour xenografts). Sera from EGFR-treated and -untreated HNSCC patients were analysed by immunoassay. RESULTS: Two independent sublines of CAL 27 and a PJ34 subline with acquired resistance to EGFR TKIs (gefitinib, erlotinib and afatinib) were developed. Resistant cells grew as highly aggressive xenografts leading to reduced host survival rates compared with EGFR-TKI sensitive cells. This suggested a link between resistance in vitro and poor prognosis in vivo. A significant upregulation of proteins linked to tumour angiogenesis and invasion was identified in resistant cells. This 'resistance-associated protein signature' (RAPS) was detected in the sera of a small cohort of HNSCC patients and was associated with reduced survival. CONCLUSION: We have identified a protein signature associated with EGFR-TKI resistance that may also be linked to poor prognosis and warrants further investigation as a potential clinical biomarker.

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[320]

**TÍTULO / TITLE:** - Anticancer mechanisms of temporin-1CEa, an amphipathic alpha-helical antimicrobial peptide, in Bcap-37 human breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Life Sci. 2013 May 30;92(20-21):1004-14. doi: 10.1016/j.lfs.2013.03.016. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1016/j.lfs.2013.03.016](http://1016/j.lfs.2013.03.016)

**AUTORES / AUTHORS:** - Wang C; Zhou Y; Li S; Li H; Tian L; Wang H; Shang D

**INSTITUCIÓN / INSTITUTION:** - Liaoning Provincial Key Laboratory of Biotechnology and Drug Discovery, Liaoning Normal University, Dalian 116029, China; Department of Pharmacy, School of Chemistry and Chemical Engineering, Liaoning Normal University, Dalian 116029, China.

**RESUMEN / SUMMARY:** - AIMS: Temporin-1CEa, a 17-residue antimicrobial peptide, is known to exert broad-spectrum anticancer activity that acts preferentially on cancer cells instead of normal cells. However, the mechanism

of cancer cell death induced by temporin-1CEa is weakly understood. MAIN METHODS: Here, we investigated the cytotoxic and membrane-disrupting effects of temporin-1CEa on human breast cancer cell line Bcap-37, using MTT assay, electronic microscope observation, fluorescence imaging and flow cytometry analysis. KEY FINDINGS: The MTT assay indicated that one-hour temporin-1CEa treatment led to rapid cell death in either caspase-dependent or -independent manner. The electronic microscope observation suggested that temporin-1CEa exposure resulted in profound morphological changes in Bcap-37 cells. The fluorescence imaging and flow cytometry analysis demonstrated that temporin-1CEa exhibited membrane-disrupting property characterized by induction of cell-surface phosphatidylserine exposure, elevation of plasma membrane permeability, and rapid transmembrane potential depolarization. Moreover, temporin-1CEa might also induce rapid cell death through mitochondria-involved mechanisms, including rapid intracellular Ca(2+) leakage, collapse of mitochondrial membrane potential ( $\Delta\psi$ ) and over-generation of reactive oxygen species (ROS). SIGNIFICANCE: In summary, the present study indicates that temporin-1CEa triggers a rapid cytotoxicity in Bcap-37 cells through membrane-destruction and intracellular mechanisms involving mitochondria. These intracellular mechanisms and direct membrane-destruction effect were evaluated helping to understand the detail action of antimicrobial peptides in mammalian cancer cells.

[321]

**TÍTULO / TITLE:** - Loss of T-Cadherin (CDH-13) Regulates AKT Signaling and Desensitizes Cells to Apoptosis in Melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 Apr 26. doi: 10.1002/mc.22018.

●●Enlace al texto completo (gratis o de pago) [1002/mc.22018](#)

**AUTORES / AUTHORS:** - Bosserhoff AK; Ellmann L; Quast AS; Eberle J; Boyle GM; Kuphal S

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, Molecular Pathology, University of Regensburg, Regensburg, Germany.

**RESUMEN / SUMMARY:** - An understanding of signaling pathways is a basic requirement for the treatment of melanoma. Currently, kinases are at the center of melanoma therapies. According to our research, additional alternative molecules are equally important for development of melanoma. In this regard, cancer progression is, among other factors, driven by an altered adhesion via cadherins. For instance, the de-regulated expression of the adhesion molecule T-cadherin is found in various cancer types, including melanoma, and influences migration and invasion. T-cadherin is thought to affect cellular function largely through its signaling and not its adhesion properties because the molecule is anchored into the cell membrane by a glycosylphosphatidylinositol (GPI) moiety. However, detailed knowledge about

the consequences of the loss of T-cadherin in melanoma is currently lacking. For this reason, we were interested in assessing which signaling pathways are initiated by T-cadherin. The tumor growth of subcutaneously injected T-cadherin-positive melanoma cells was diminished compared with T-cadherin-negative cells in nude mice. The difference in tumor volume was not due to decreased proliferation but rather due to increased apoptosis. After the expression of T-cadherin was induced, we detected V-AKT murine thymoma viral oncogene homolog (AKT) and FoxO3a hypophosphorylation accompanied by the downregulation of the antiapoptotic molecules BCL-2, BCL-x and Clusterin. Furthermore, we detected a diminished transcriptional activity of CREB and AP-1. We demonstrated that T-cadherin functions as a pro-apoptotic tumor suppressor that antagonizes AKT/CREB/AP-1/FoxO3a signaling, whereas NFkappaB, TCF/LEF and mTOR are not part of the T-cadherin signaling pathway. Notably, we found that the restoration of T-cadherin in melanoma cells causes sensitization to apoptosis induced by CD95/Fas antibody CH-11. © 2013 Wiley Periodicals, Inc.

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[322]

**TÍTULO / TITLE:** - Design and Synthesis of Dual-Action Inhibitors Targeting Histone Deacetylases and 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase for Cancer Treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Chem. 2013 May 9;56(9):3645-55. doi: 10.1021/jm400179b. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1021/jm400179b](http://1021/jm400179b)

**AUTORES / AUTHORS:** - Chen JB; Chern TR; Wei TT; Chen CC; Lin JH; Fang JM

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, National Taiwan University, Taipei 106, Taiwan.

**RESUMEN / SUMMARY:** - A series of dual-action compounds were designed to target histone deacetylase (HDAC) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) by having a hydroxamate group essential for chelation with the zinc ion in the active site of HDAC and the key structural elements of statin for binding with both proteins. In our study, the statin hydroxamic acids prepared by a fused strategy are most promising in cancer treatments. These compounds showed potent inhibitory activities against HDACs and HMGR with IC50 values in the nanomolar range. These compounds also effectively reduced the HMGR activity as well as promoted the acetylations of histone and tubulin in cancer cells, but were not toxic to normal cells.

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[323]

**TÍTULO / TITLE:** - The proteasome inhibitor lactacystin exerts its therapeutic effects on glioma via apoptosis: an in vitro and in vivo study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Int Med Res. 2013 Feb;41(1):72-81. doi: 10.1177/0300060513476992. Epub 2013 Jan 24.

●●Enlace al texto completo (gratis o de pago)

[1177/0300060513476992](#)

**AUTORES / AUTHORS:** - Wang H; Zhang S; Zhong J; Zhang J; Luo Y; Pengfei G

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, First Bethune Hospital of Jilin University, Changchun, Jilin Province, China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To examine the effect and underlying mechanism of action of the proteasome inhibitor lactacystin on glioma, in vitro and in vivo. **METHODS:** Rat C6 glioma cells were cultured with or without lactacystin. Cell proliferation, apoptosis and mitochondrial membrane potential were determined. A glioma xenograft model was established in mice and animals were treated with 0, 1 or 5 microg/20 g body weight lactacystin for 7 days. Animals were sacrificed on day 17 after completion of treatment. Apoptosis in tumour tissue was examined by terminal deoxynucleotidyl transferase dUTP nick end labeling staining. Levels of B cell lymphoma 2 (Bcl-2), and Bcl2-associated X protein (Bax) protein and mRNA, were determined in C6 cells and tumour tissues. **RESULTS:** Lactacystin significantly inhibited the proliferation of C6 cells, increased apoptosis and reduced mitochondrial membrane potential in vitro, and suppressed tumour growth in vivo. Lactacystin increased the ratio of Bax to Bcl-2 at the mRNA and protein levels, both in vitro and in vivo. **CONCLUSIONS:** The effects of lactacystin are associated with apoptosis induction. Proteasome inhibition may represent an effective treatment option for glioma.

[324]

**TÍTULO / TITLE:** - Epirubicin and docetaxel as first-line treatment for hormonal receptor positive metastatic breast cancer: the predictive value of luminal subtype: A retrospective cohort analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Chemother. 2013;25(2):112-8. doi: 10.1179/1973947812Y.0000000059.

●●Enlace al texto completo (gratis o de pago)

[1179/1973947812Y.0000000059](#)

**AUTORES / AUTHORS:** - Nelli F; Natoli G; Moscetti L; Massari A; D'Auria G; Fabbri MA; Frittelli P; Ruggeri EM

**INSTITUCIÓN / INSTITUTION:** - Central Hospital of Belcolle, Viterbo, Italy.

**RESUMEN / SUMMARY:** - **BACKGROUND:** We retrospectively evaluated the efficacy of first-line epirubicin and docetaxel in patients with metastatic, hormonal receptor (HR)-positive, and human epidermal growth factor receptor-2-negative breast cancer. A subgroup analysis evaluated the predictive value of immunohistochemistry-defined luminal subtype. **METHODS:** We included

patients with at least one visceral and measurable site of metastatic disease. Patients were grouped as luminal A (HR(+) and Ki67<13%) or luminal B (HR(+) and Ki67>13%). RESULTS: Forty-four patients were entered and prognostic variables were similar between the subgroups. Luminal B patients achieved higher objective response rate than luminal A (69% versus 19%; P = 0.001), longer time to progression (12.2 months versus 8.6 months; P = 0.039), and longer overall survival (24.6 months versus 19.5 months; P = 0.041). The multivariate analysis confirmed the predictive value of luminal B subtype for longer time to progression. CONCLUSIONS: Identification by Ki67 labelling index of human epidermal growth factor receptor-2-negative luminal A could predict a substantial benefit from systemic chemotherapy. Endocrine therapy would be the most appropriate therapy for luminal A tumours.

[325]

**TÍTULO / TITLE:** - Induction of the liver cancer-down-regulated long noncoding RNA uc002mbe.2 mediates trichostatin-induced apoptosis of liver cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Pharmacol. 2013 May 1. pii: S0006-2952(13)00262-1. doi: 10.1016/j.bcp.2013.04.020.

●●Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.04.020](http://1016/j.bcp.2013.04.020)

**AUTORES / AUTHORS:** - Yang H; Zhong Y; Xie H; Lai X; Xu M; Nie Y; Liu S; Wan YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Second Affiliated Hospital, Guangzhou Medical University, Guangzhou, China. Electronic address: [yanghui030454@gmail.com](mailto:yanghui030454@gmail.com).

**RESUMEN / SUMMARY:** - Differential expression of long non-coding RNAs (lncRNAs) plays critical roles in hepatocarcinogenesis. Considerable attention has focused on the antitumor effect of histone deacetylase inhibitor (Trichostatin A, TSA) as well as the coding gene expression-induced apoptosis of cancer cells. However, it is not known whether lncRNA has a role in TSA-induced apoptosis of human hepatocellular carcinoma (HCC) cells. The global expression of lncRNAs and coding genes was analyzed with the Human LncRNA Array V2.0 after 24h treatment. Expression was verified in cell lines and tissues by quantitative real-time PCR. The data showed that 4.8% (959) of lncRNA and 6.1% (1849) of protein coding gene were significantly differentially expressed. The differential expressions of lncRNA and protein coding genes had distinguishable hierarchical clustering expression profiling pattern. Among these differentially expressed lncRNAs, the greatest change was noted for uc002mbe.2, which had more than 300 folds induction upon TSA treatment. TSA selectively induced uc002mbe.2 in four studied HCC cell lines. Compared with normal human hepatocytes and adjacent noncancerous tissues, uc002mbe.2 expression level was significantly lower in the HCC cell lines and liver cancer tissues. The TSA-induced uc002mbe.2 expression was positively

correlated with the apoptotic effect of TSA in HCC cells. In addition, knockdown the expression of uc002mbe.2 significantly reduced TSA-induced apoptosis of Huh7 cells. Therefore, TSA-induced apoptosis of HCC cells is uc002mbe.2 dependent and reduced expression of uc002mbe.2 may be associated with liver carcinogenesis.

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[326]

**TÍTULO / TITLE:** - Protective Role of the Inflammatory CCR2/CCL2 Chemokine Pathway through Recruitment of Type 1 Cytotoxic gamma delta T Lymphocytes to Tumor Beds.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Immunol. 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [4049/jimmunol.1300434](http://4049/jimmunol.1300434)

**AUTORES / AUTHORS:** - Lanca T; Costa MF; Goncalves-Sousa N; Rei M; Grosso AR; Penido C; Silva-Santos B

**INSTITUCIÓN / INSTITUTION:** - Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, 1649-028 Lisbon, Portugal;

**RESUMEN / SUMMARY:** - Tumor-infiltrating lymphocytes (TILs) are important prognostic factors in cancer progression and key players in cancer immunotherapy. Although gamma delta T lymphocytes can target a diversity of tumor cell types, their clinical manipulation is hampered by our limited knowledge of the molecular cues that determine gamma delta T cell migration toward tumors in vivo. In this study we set out to identify the chemotactic signals that orchestrate tumor infiltration by gamma delta T cells. We have used the preclinical transplantable B16 melanoma model to profile chemokines in tumor lesions and assess their impact on gamma delta TIL recruitment in vivo. We show that the inflammatory chemokine CCL2 and its receptor CCR2 are necessary for the accumulation of gamma delta TILs in B16 lesions, where they produce IFN-gamma and display potent cytotoxic functions. Moreover, CCL2 directed gamma delta T cell migration in vitro toward tumor extracts, which was abrogated by anti-CCL2 neutralizing Abs. Strikingly, the lack of gamma delta TILs in TCRdelta-deficient but also in CCR2-deficient mice enhanced tumor growth in vivo, thus revealing an unanticipated protective role for CCR2/CCL2 through the recruitment of gamma delta T cells. Importantly, we demonstrate that human Vdelta1 T cells, but not their Vdelta2 counterparts, express CCR2 and migrate to CCL2, whose expression is strongly deregulated in multiple human tumors of diverse origin, such as lung, prostate, liver, or breast cancer. This work identifies a novel protective role for CCL2/CCR2 in the tumor microenvironment, while opening new perspectives for modulation of human Vdelta1 T cells in cancer immunotherapy.

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[327]

**TÍTULO / TITLE:** - Identification of alpha1-antitrypsin as a potential prognostic biomarker for advanced nonsmall cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors by proteomic analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Int Med Res. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago)

[1177/0300060513476582](#)

**AUTORES / AUTHORS:** - Zhao W; Yang Z; Liu X; Tian Q; Lv Y; Liang Y; Li C; Gao X; Chen L

**INSTITUCIÓN / INSTITUTION:** - Respiratory Institute, People's Liberation Army General Hospital, Beijing, China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** This retrospective study attempted to identify serum biomarkers that could help to indicate treatment response in advanced nonsmall-cell lung cancer (NSCLC) patients receiving epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment. **METHODS:** Two-dimensional fluorescence difference gel electrophoresis and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry were used to identify proteins expressed in serum samples from NSCLC patients with long (>6-month) progression-free survival (PFS) periods, following EGFR-TKI treatment. **RESULTS:** Serum amyloid P component (APCS), alpha1-antitrypsin (AAT), fibrinogen-alpha (FGA), keratin type I cytoskeletal 10 (KRT10) and serotransferrin (TF) expression differed between samples taken from 18 patients before treatment (baseline) and when progressive disease (PD) was observed, during treatment. Changes in AAT, KRT10 and APCS levels were validated by Western blot analysis in the sample pool; findings were further validated by Western blot analysis in a random sample of four patients. These proteins were also present in serum samples obtained from the same patients at the partial response (PR) timepoint during EGFR-TKI treatment. AAT was upregulated at PD compared with baseline, but downregulated during the PR phase. **CONCLUSION:** These observations suggest that AAT could be used as a serological biomarker for predicting the utility of EGFR-TKI treatment for advanced NSCLC.

[328]

**TÍTULO / TITLE:** - Nuclear EGFR protein expression predicts poor survival in early stage non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Apr 26. pii: S0169-5002(13)00146-3. doi: 10.1016/j.lungcan.2013.03.020.

●●Enlace al texto completo (gratis o de pago)

[1016/j.lungcan.2013.03.020](#)

**AUTORES / AUTHORS:** - Traynor AM; Weigel TL; Oettel KR; Yang DT; Zhang C; Kim K; Salgia R; Iida M; Brand TM; Hoang T; Campbell TC; Hernan HR; Wheeler DL

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine and Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA.

**RESUMEN / SUMMARY:** - INTRODUCTION: Nuclear EGFR (nEGFR) has been identified in various human tumor tissues, including cancers of the breast, ovary, oropharynx, and esophagus, and has predicted poor patient outcomes. We sought to determine if protein expression of nEGFR is prognostic in early stage non-small cell lung cancer (NSCLC). METHODS: Resected stages I and II NSCLC specimens were evaluated for nEGFR protein expression using immunohistochemistry (IHC). Cases with at least one replicate core containing  $\geq 5\%$  of tumor cells demonstrating strong dot-like nucleolar EGFR expression were scored as nEGFR positive. RESULTS: Twenty-three (26.1% of the population) of 88 resected specimens stained positively for nEGFR. Nuclear EGFR protein expression was associated with higher disease stage (45.5% of stage II vs. 14.5% of stage I;  $p=0.023$ ), histology (41.7% in squamous cell carcinoma vs. 17.1% in adenocarcinoma;  $p=0.028$ ), shorter progression-free survival (PFS) (median PFS 8.7 months [95% CI 5.1-10.7 mo] for nEGFR positive vs. 14.5 months [95% CI 9.5-17.4 mo] for nEGFR negative; hazard ratio (HR) of 1.89 [95% CI 1.15-3.10];  $p=0.011$ ), and shorter overall survival (OS) (median OS 14.1 months [95% CI 10.3-22.7 mo] for nEGFR positive vs. 23.4 months [95% CI 20.1-29.4 mo] for nEGFR negative; HR of 1.83 [95% CI 1.12-2.99];  $p=0.014$ ). CONCLUSIONS: Expression of nEGFR protein was associated with higher stage and squamous cell histology, and predicted shorter PFS and OS, in this patient cohort. Nuclear EGFR serves as a useful independent prognostic variable and as a potential therapeutic target in NSCLC.

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[329]

**TÍTULO / TITLE:** - Tubulin-beta-III overexpression by uterine serous carcinomas is a marker for poor overall survival after platinum/taxane chemotherapy and sensitivity to epothilones.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer. 2013 Apr 12. doi: 10.1002/cncr.28017.

●●Enlace al texto completo (gratis o de pago) [1002/cncr.28017](#)

**AUTORES / AUTHORS:** - Roque DM; Bellone S; English DP; Buza N; Cocco E; Gasparini S; Bortolomai I; Ratner E; Silasi DA; Azodi M; Rutherford TJ; Schwartz PE; Santin AD

**INSTITUCIÓN / INSTITUTION:** - Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut.

**RESUMEN / SUMMARY:** - BACKGROUND: Uterine serous carcinoma (USC) is a subtype of endometrial cancer associated with chemoresistance and poor outcome. Overexpression of tubulin-beta-III and p-glycoprotein has been linked to paclitaxel resistance in many cancers but has been undercharacterized among USCs. Epothilones have demonstrated activity in certain paclitaxel-resistant malignancies. In this study, relationships are clarified, in USCs relative to ovarian serous carcinomas (OSCs), between tubulin-beta-III and p-glycoprotein expression, clinical outcome, and in vitro chemoresponsiveness to epothilone B, ixabepilone, and paclitaxel. METHODS: Tubulin-beta-III and p-glycoprotein were quantified by real-time polymerase chain reaction in 48 fresh-frozen tissue samples and 13 cell lines. Copy number was correlated with immunohistochemistry and overall survival. Median inhibitory concentration (IC50) was determined using viability and metabolic assays. Impact of tubulin-beta-III knockdown on IC50 was assessed with small interfering RNAs. RESULTS: USC overexpressed tubulin-beta-III but not p-glycoprotein relative to OSC in both fresh-frozen tissues (552.9 +/- 106.7 versus 202.0 +/- 43.99, P = .01) and cell lines (1701.0 +/- 376.4 versus 645.1 +/- 157.9, P = .02). Tubulin-beta-III immunohistochemistry reflected quantitative real-time polymerase chain reaction copy number and overexpression stratified patients by overall survival (copy number <= 400: 615 days; copy number > 400: 165 days, P = .049); p-glycoprotein did not predict clinical outcome. USCs remained exquisitely sensitive to patupilone in vitro despite tubulin-beta-III overexpression (IC50,USC 0.245 +/- 0.11 nM versus IC50,OSC 1.01 +/- 0.13 nM, P = .006). CONCLUSIONS: Tubulin-beta-III overexpression in USCs discriminates poor prognosis, serves as a marker for sensitivity to epothilones, and may contribute to paclitaxel resistance. Immunohistochemistry reliably identifies tumors with overexpression of tubulin-beta-III, and a subset of individuals likely to respond to patupilone and ixabepilone. Epothilones warrant clinical investigation for treatment of USCs. Cancer 2013;000:000-000. © 2013 American Cancer Society.

[330]

**TÍTULO / TITLE:** - A population study showing that the advent of second generation tyrosine kinase inhibitors has improved progression-free survival in chronic myeloid leukaemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 Jul;37(7):752-8. doi: 10.1016/j.leukres.2013.04.003. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.04.003](http://1016/j.leukres.2013.04.003)

**AUTORES / AUTHORS:** - Francis S; Lucas C; Lane S; Wang L; Watmough S; Knight K; Bell J; Kaleel-Rahman M; Lee E; O'Brien D; Butt NM; Sadik W; De Soysa L; Seale JR; Salim R; Clark RE

**INSTITUCIÓN / INSTITUTION:** - Haematology Department, Royal Liverpool University Hospital, Liverpool, UK. Electronic address: [Sebastian.Francis@liv.ac.uk](mailto:Sebastian.Francis@liv.ac.uk).

**RESUMEN / SUMMARY:** - BACKGROUND: Population based data suggest the proportion of patients failing imatinib in chronic myeloid leukaemia (CML) is higher than the reported one-third of patients in clinical trials. Clinical trials have demonstrated second generation tyrosine kinase inhibitors (TKI) dasatinib and nilotinib can restore complete cytogenetic remission (CCR) and major molecular response (MMR) to many patients failing imatinib, but their impact in the general population is not clear. DESIGN AND METHODS: We report CML outcome in a population of 2.3 million people in a geographically contiguous area of North West England and North Wales. RESULTS: Between 2003 and 2009, 192 new CML cases were diagnosed, of whom 184 were in chronic phase and 160 started on imatinib. The maximal CCR rate was 65% at 24 months and the maximal MMR rate was 50% at 36 months. Patients diagnosed since second generation TKI became available for imatinib failure had a more rapid cumulative CCR and MMR rate and a significantly improved progression free survival ( $p=0.022$ ) than those diagnosed before this time. CONCLUSION: The study indicates that second generation TKI have improved CML outcome in the general population.

[331]

**TÍTULO / TITLE:** - Vascular endothelial growth factor receptors 1,3 and caveolin-1 are implicated in colorectal cancer aggressiveness and prognosis-correlations with epidermal growth factor receptor, CD44v6, focal adhesion kinase, and c-Met.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0776-](#)

[1](#)

**AUTORES / AUTHORS:** - Garouniatis A; Zizi-Sermpetzoglou A; Rizos S; Kostakis A; Nikiteas N; Papavassiliou AG

**INSTITUCIÓN / INSTITUTION:** - Department of General Medicine, "G. Gennimatas" General Hospital, Athens, Greece.

**RESUMEN / SUMMARY:** - Vascular endothelial growth factor receptor-1 (VEGFR-1) and caveolin-1 have been shown to act both as tumor-promoting and tumor-suppressing proteins in various malignancies as well as in colorectal cancer (CRC), while VEGFR-3's lymphangiogenic involvement and connection to tumor parameters has yielded heterogenic results. This study was designed to investigate the expression of these molecules in 183 human CRC tissue specimens and explore their effect in both clinicopathological parameters and disease prognosis. We also utilize our previous results regarding epidermal growth factor receptor (EGFR), c-Met, CD44v6, and focal adhesion kinase, in

an attempt to further clarify their distinct role in tumor prognosis and their crosstalk. Caveolin-1 was more freely distributed in the neoplasms of the right colon and restricted towards the left and the rectal cancer samples ( $p = 0.022$ ); VEGFR-3 was associated with higher nodal metastasis' status ( $p = 0.001$ ) and staging ( $p = 0.006$ ), and loss of VEGFR-1 predicted distant metastasis ( $p = 0.026$ ) and advanced stage ( $p = 0.049$ ). Prompted by previous reports, we performed all analyses also in the patient group of early (I and II) tumor stage where it was evident that VEGFR-1 was more frequently expressed in patients under 60 years old ( $p = 0.014$ ) and VEGFR-3 was significantly elevated in left colon cancers ( $p = 0.039$ ) and female patients ( $p = 0.038$ ). Within the advanced stage (III and IV), the absence of VEGFR-1 exhibited a tendency for higher M status ( $p = 0.067$ ) and lack of caveolin-1 signified worse AJCC classification ( $p = 0.053$ ). Additionally, patient survival was influenced from VEGFR-3 ( $p = 0.019$ ) for the whole sample, whereas subgroup analyses provided a correlation between caveolin-1 expression and improved survival in the early detection group of patients ( $p = 0.022$ ). Using Cox regression for all available markers, EGFR, CD44v6, and VEGFR-1 emerged in this study as potential surrogate markers, the latter having positive prognostic significance. We further explored the multiple receptor correlations that were identified.

[332]

**TÍTULO / TITLE:** - Azidothymidine hinders arsenic trioxide-induced apoptosis in acute promyelocytic leukemia cells by induction of p21 and attenuation of G2/M arrest.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 May 5.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1763-8](http://1007/s00277-013-1763-8)

**AUTORES / AUTHORS:** - Hassani S; Ghaffari SH; Zaker F; Mirzaee R; Mardani H; Bashash D; Zekri A; Yousefi M; Zaghali A; Alimoghaddam K; Ghavamzadeh A

**INSTITUCIÓN / INSTITUTION:** - Hematology, Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

**RESUMEN / SUMMARY:** - To enhance anticancer efficacy of the arsenic trioxide (ATO), the combination of ATO and azidothymidine (AZT), with convergence anti-telomerase activity, were examined on acute promyelocytic leukemia (APL) cell line, NB4. In spite of an induction of apoptosis by both drugs separately and a synergistic effect of them on hTERT down-regulation and telomerase inhibition, the ATO-induced cytotoxicity was reduced when it was used in combination with AZT. AZT attenuated the ATO effects on viability, metabolic activity, DNA synthesis, and apoptosis. These observations, despite the deflection from the main goal of this study, dedicate an especial opportunity to elucidate the importance of some of the mechanisms that have been suggested

by which ATO induces apoptosis. Cell cycle distribution, ROS level, and caspase-3 activation analyses suggest that AZT reduced the ATO-induced cytotoxic effect possibly via relative induction and diminution of cells accumulated in (G1, S) and (G2/M) phase, respectively, as well as through attenuation of ROS generation and subsequent caspase-3 inhibition. QRT-PCR assay revealed that induction of p21 expression by the combined AZT/ATO compared to ATO alone could be a reason for the relative decline of cells accumulation in G2/M and the increase of cells in G1 and S phases. Therefore, the G2/M arrest and ROS generation are likely principle mediators for the ATO-induced apoptosis and can be used as a guide to design rational combinatorial strategies involving ATO and agents with G2/M arrest or ROS generation capacity to intensify ATO-induced apoptosis.

[333]

**TÍTULO / TITLE:** - Clinical neuropathology practice guide 3-2013: levels of evidence and clinical utility of prognostic and predictive candidate brain tumor biomarkers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Neuropathol. 2013 May-Jun;32(3):148-58.

**AUTORES / AUTHORS:** - Berghoff AS; Stefanits H; Woehrer A; Heinzl H; Preusser M; Hainfellner JA

**INSTITUCIÓN / INSTITUTION:** - Institute of Neurology, Department of Neurosurgery, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Austria.

**RESUMEN / SUMMARY:** - A large number of potential tissue biomarkers has been proposed for brain tumors. However, hardly any have been adopted for routine clinical use, so far. For most candidate biomarkers substantial controversy exists with regard to their usefulness in clinical practice. The multidisciplinary neurooncology taskforce of the Vienna Comprehensive Cancer Center Central Nervous System Unit (CCC-CNS) addressed this issue and elaborated a four-tiered levels-of-evidence system for assessing analytical performance (reliability of test result) and clinical performance (prognostic or predictive) based on consensually defined criteria. The taskforce also consensually agreed that only biomarker candidates should be considered as ready for clinical use, which meet defined quality standards for both, analytical and clinical performance. Applying this levels-of-evidence system to MGMT, IDH1, 1p19q, Ki67, MYCC, MYCN and beta-catenin, only immunohistochemical IDH1 mutation testing in patients with diffuse gliomas is supported by sufficient evidence in order to be unequivocally qualified for clinical use. For the other candidate biomarkers lack of published evidence of sufficiently high analytical test performance and, in some cases, also of clinical performance limits evidence-based confirmation of their clinical utility. For most of the markers, no common standard of laboratory testing exists. We conclude that, at present, there is a strong need for studies

that specifically address the analytical performance of candidate brain tumor biomarkers. In addition, standardization of laboratory testing is needed. We aim to regularly challenge and update the present classification in order to systematically clarify the current translational status of candidate brain tumor biomarkers and to identify specific research needs for accelerating the translational pace.

[334]

**TÍTULO / TITLE:** - Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics and prognosis in gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Gastroenterol. 2013 Apr 14;19(14):2171-8. doi: 10.3748/wjg.v19.i14.2171.

●●Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i14.2171](#)

**AUTORES / AUTHORS:** - He C; Bian XY; Ni XZ; Shen DP; Shen YY; Liu H; Shen ZY; Liu Q

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200127, China.

**RESUMEN / SUMMARY:** - AIM: To investigate human epidermal growth factor receptor 2 (HER2) gene amplification and protein expression in Chinese patients with resectable gastric cancer and the association with clinicopathological characteristics and survival. METHODS: One hundred and ninety-seven gastric cancer patients who underwent curative surgery procedures were enrolled into this study. HER2 gene amplification and protein expression were examined using fluorescence in-situ hybridization (FISH) and immunohistochemistry (IHC) analysis on formalin-fixed paraffin-embedded gastric cancer samples from all patients. For scoring, Hofmann's HER2 gastric cancer scoring system was adopted. All cases showing IHC3+ or FISH positivity were defined as HER2 positive. Patient clinicopathological data and survival information were collected. Finally, chi(2) statistical analysis was performed to analyze the HER2 positivity rate amongst the subgroups with different clinicopathological characteristics including; gender, age, tumor location, Lauren classification, differentiation, TNM staging, depth of invasion, lymph node metastases and distant metastasis. The probability of survival for different subgroups with different clinicopathological characteristics was calculated using the Kaplan-Meier method and survival curves plotted using log rank inspection. RESULTS: According to Hofmann's HER2 gastric cancer scoring criteria, 31 cases (15.74%) were identified as HER2 gene amplified and 19 cases (9.64%) were scored as strongly positive for HER2 membrane staining (3+), 25 cases (12.69%) were moderately positive (2+) and 153 cases (77.66%) were HER2 negative (0/1+). The concordance rate between IHC and FISH analyses was 88.83% (175/197). Thirty-six cases were defined as positive for HER2 gene

amplification and/or protein expression, with 24 of these cases being eligible for Herceptin treatment according to United States recommendations, and 29 of these cases eligible according to EU recommendations. Highly consistent results were detected between IHC3+, IHC0/1 and FISH (73.68% and 95.42%), but low consistency was observed between IHC2+ and FISH (40.00%). The positivity rates in intestinal type and well-differentiated gastric cancer were higher than those in diffuse/mixed type and poorly-differentiated gastric cancer respectively (28.57% vs 13.43%,  $P = 0.0103$ ; 37.25% vs 11.64%,  $P < 0.0001$ ), but were not correlated with gender, age, tumor location or TNM stage, depth of invasion, lymph node metastases and distant metastasis. In poorly-differentiated gastric cancer patients, those without lymph node metastasis showed a higher HER2 positivity rate than those with lymph node metastasis (26.47% vs 7.14%,  $P = 0.0021$ ). This association was not present in those patients with well-differentiated gastric cancer (28.57% vs 43.33%,  $P = 0.2832$ ). Within our patient cohort, 26 cases were lost to follow-up. The median survival time for the remaining 171 patients was 18 mo. The median survival times of the HER2 positive and negative groups were 17 and 18.5 mo respectively. Overall survival was not significantly different between HER2-positive and negative groups ( $\chi^2(2) = 0.9157$ ,  $P = 0.3386$ ), but in patients presenting well-differentiated tumors, the overall survival of the HER2-positive group was significantly worse than that of the HER2-negative group ( $P = 0.0123$ ). In contrast, patients with poorly differentiated and diffuse/mixed subtype gastric cancers showed no significant differences in overall survival associated with HER2. Furthermore, the median survival time of the HER2 positive group did not show any statistically significant differences when compared to the subgroups of gender, age, tumor location, TNM classification, lymph node metastases and distant metastasis. CONCLUSION: Patients with intestinal type gastric cancer (GC), well-differentiated GC and poorly-differentiated GC without lymph node metastasis, may all represent suitable candidates for targeted therapy using Herceptin.

[335]

**TÍTULO / TITLE:** - The Correlation Between Dose of Folinic Acid and Neurotoxicity in Children and Adolescents Treated for Osteosarcoma With High-dose Methotrexate (HDMTX): A Neuropsychological and Psychosocial Study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pediatr Hematol Oncol. 2013 May;35(4):271-5. doi: 10.1097/MPH.0b013e31828c2da1.

●●Enlace al texto completo (gratis o de pago)

[1097/MPH.0b013e31828c2da1](#)

**AUTORES / AUTHORS:** - Bonda-Shkedi E; Arush MW; Kaplinsky C; Ash S; Goshen Y; Yaniv I; Cohen IJ

**INSTITUCIÓN / INSTITUTION:** - \*Department of Hematology Oncology, Schneider Children's Medical Center of Israel, Petah Tikva daggerDepartment of Psychology, Hebrew University of Jerusalem, Jerusalem double daggerMeyer Children's Hospital, Rambam Medical Center, Haifa section signThe Edmond and Lily Safra Childrens Hospital, Chaim Sheba Medical Center, Ramat Gan parallelSackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel.

**RESUMEN / SUMMARY:** - BACKGROUND: : This study has been performed to examine the currently used doses of folinic acid (FA) and to determine the importance of the dose of FA in preventing subtle neurotoxicity. Thirty osteosarcoma patients were an appropriate population studied as they have no intrinsic neurological involvement. The neuropsychological and psychosocial status was tested in 2 groups of patients treated with similar protocols containing repeated doses of high-dose methotrexate, but different doses of FA. The patients received 300 to 600 mg/m or 120 to 250 mg/m FA in their protocols. METHODS: : Eighteen tests or subtests of neuropsychological assessment were tested. RESULTS: : Eleven of 18 tests were significant at the  $P=0.025$  level favoring the group treated with high dose of FA. There were no clear results in the psychosocial measures with only a single measure of self-esteem (understanding) being significantly higher ( $P=0.024$ ) in the group treated with high dose of FA, other measures had no statistical significance. CONCLUSIONS: : A correlation between a higher dose of FA after high-dose methotrexate and a better neuropsychological status was clearly shown. The doses of FA used in the low FA group, 120 to 250 mg/m, were similar to those used by several groups treating children with leukemia; some have used even lower doses and report gross neurotoxicity.

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[336]

**TÍTULO / TITLE:** - The prognostic impact of human leukocyte antigen (HLA) class I antigen abnormalities in salivary gland cancer. A clinicopathological study of 288 cases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Histopathology. 2013 May;62(6):847-59. doi: 10.1111/his.12086.

●●Enlace al texto completo (gratis o de pago) [1111/his.12086](#)

**AUTORES / AUTHORS:** - Muller M; Agaimy A; Zenk J; Ettl T; Iro H; Hartmann A; Seliger B; Schwarz S

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, University of Erlangen, Erlangen, Germany.

**RESUMEN / SUMMARY:** - AIMS: To study abnormalities of proteins of the major histocompatibility complex class I in a series of 288 salivary gland carcinomas, and to correlate findings with patients' overall survival (OS). METHODS AND RESULTS: Protein expression of human leukocyte antigen (HLA)-A, heavy chain (HC)-10, beta2 -microglobulin, low molecular weight polypeptides (LMP) 2

and 7, transporters associated with antigen processing (TAP) 1 and 2, calnexin, calreticulin, endoplasmic reticulum (ER) p57 and tapasin was evaluated by immunohistochemistry and semiquantitatively analyzed. As compared with normal salivary gland tissue, HLA-A, LMP7, TAP2 and HLA class I were significantly down-regulated in salivary gland carcinomas, whereas beta2 - microglobulin, calnexin, LMP2, and TAP1 were upregulated. Expression of calreticulin, ERp57 and tapasin was unaltered. In univariate Kaplan-Meier analyses, low expression of LMP7 (P = 0.005) and high expression of beta2 - microglobulin (P = 0.028), HLA-A (P < 0.001), TAP1 (P = 0.01), and tapasin (P < 0.001) were significantly associated with shorter OS. In multivariate analysis incorporating tumour stage, nodal/distant metastasis, and grade, HLA-A (P = 0.014), LMP7 (P = 0.033), and tapasin (P = 0.024), as well as distant metastasis (P = 0.012) and high tumour grade (P < 0.001), remained statistically significant. CONCLUSION: The prognostic influence of up-regulated HLA-A and tapasin and down-regulated LMP7 may provide a rationale for targeting these specific components of the antigen processing and presentation pathway in salivary gland carcinomas.

[337]

**TÍTULO / TITLE:** - p53 interferes with microtubule-stabilizing agent-induced apoptosis in prostate and colorectal cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Jun;31(6):1388-94. doi: 10.3892/ijmm.2013.1333. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1333](#)

**AUTORES / AUTHORS:** - Kim JY; Chung JY; Lee SG; Kim YJ; Park JE; Yun J; Park YC; Kim BG; Yoo YH; Kim JM

**INSTITUCIÓN / INSTITUTION:** - Department of Anatomy and Cell Biology, Dong-A University, Busan, Republic of Korea.

**RESUMEN / SUMMARY:** - Taxanes are microtubule-stabilizing agents that have anticancer activity against several types of human solid tumors. Although the primary mechanism of action of these drugs is well understood, the signaling pathways that confer resistance to these agents in certain types of cancer remain poorly understood. In particular, the association of p53 with the mechanism(s) of taxane-mediated cell death is still controversial. In this study, we showed that p53 has a profound inhibitory effect on docetaxel (Doc)-induced apoptosis in prostate and colorectal cancer cells and that caspases play a critical role in this process. Doc induced prostate cancer cell apoptosis at high levels in p53-null PC3 cells, at intermediate levels in p53-mutant DU145 cells and at low levels in p53 wild-type LNCaP cells. While transient overexpression of p53 in PC3 cells suppressed Doc-induced apoptosis, knockdown of p53 in LNCaP cells increased apoptosis. This finding was further confirmed using an isogenic pair of colorectal cancer cell lines, HCT-116 p53-/-

and p53+/+, indicating that p53 inhibits induction of apoptosis by Doc. To our knowledge, this is the first report describing that chemical or genetic knockout of p53 enhances the susceptibility of both prostate and colorectal cancer cells to Doc-induced apoptosis. These results may suggest an approach to stratify patients for regimens involving Doc.

[338]

**TÍTULO / TITLE:** - Ischaemic Colitis in Rheumatoid Arthritis Patients Receiving Tumour Necrosis Factor-alpha Inhibitors: An Analysis of Reports to the US FDA Adverse Event Reporting System.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Drug Saf. 2013 May;36(5):329-34. doi: 10.1007/s40264-013-0041-y.

●●Enlace al texto completo (gratis o de pago) [1007/s40264-013-0041-](#)

[y](#)

**AUTORES / AUTHORS:** - Salk A; Stobaugh DJ; Deepak P; Ehrenpreis ED

**INSTITUCIÓN / INSTITUTION:** - Center for the Study of Complex Diseases, Research Institute, North Shore University Health System, 1001 University Place, Evanston, IL, 60201, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Tumour necrosis factor-alpha (TNF-alpha) inhibitors are immunosuppressants, approved for the treatment and maintenance of rheumatoid arthritis (RA). Immunosuppression has been shown to induce ischaemic colitis (IC) in an animal model; however, a relationship between TNF inhibitors and IC has rarely been reported in the published literature. OBJECTIVE: The aim of this study was to better characterize the association between TNF-alpha inhibitors with IC in RA patients, by analysing adverse event reports submitted to the US FDA Adverse Event Reporting System (AERS) and the published literature. METHODS: The FDA AERS database was searched and we identified all reports between January 2003 and June 2011. The search was limited to an indication of RA, a 'primary suspect' drug of TNF-alpha inhibitors and a reaction of IC. Full-length reports were obtained and analysed utilizing the Freedom of Information Act. The cases were organized by age, sex, type of TNF-alpha inhibitor, concomitant drugs and medical co-morbidities. Cases were labelled as definite, probable, possible or doubtful drug-induced adverse events based on the Naranjo Scale. A PubMed search was performed to obtain published literature documenting events of anti-TNF-associated IC. RESULTS: Twelve cases were eliminated because of more likely causes for IC. Thirty-five primary suspect reports of TNF-alpha inhibitors associated with IC in RA patients were identified in the FDA AERS. Thirteen cases were reported with infliximab, 12 with adalimumab, 7 with etanercept and 3 with certolizumab. The majority of the cases were in females (29/35) and those between the ages of 50 and 65 years (18/35). Use of the Naranjo Scale revealed 17 probable and 18 possible cases of anti-TNF-induced

IC. In the literature, one report of IC associated with adalimumab was identified.  
CONCLUSION: TNF-alpha inhibitors may be initiating factors or co-factors in the development of IC in RA patients, and further research to determine the mechanism of this association is warranted.

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[339]

**TÍTULO / TITLE:** - Juglone, isolated from *Juglans mandshurica* Maxim, induces apoptosis via down-regulation of AR expression in human prostate cancer LNCaP cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Jun 15;23(12):3631-4. doi: 10.1016/j.bmcl.2013.04.007. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.04.007](http://1016/j.bmcl.2013.04.007)

**AUTORES / AUTHORS:** - Xu H; Yu X; Qu S; Sui D

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, School of Pharmaceutical Sciences, Jilin University, 1266 Fujin Rd., Changchun, Jilin Province 130021, PR China.

**RESUMEN / SUMMARY:** - Juglone is a natural compound which has been isolated from *Juglans mandshurica* Maxim. Recent studies have shown that juglone had various pharmacological effects such as anti-viral, anti-bacterial and anti-cancer. However, its anti-cancer activity on human prostate cancer LNCaP cell has not been examined. Thus, the current study was designed to elucidate the molecular mechanism of apoptosis induced by juglone in androgen-sensitive prostate cancer LNCaP cells. MTT assay was performed to examine the anti-proliferative effect of juglone. Occurrence of apoptosis was detected by Hoechst 33342 staining and flow cytometry in LNCaP cells treated with juglone for 24h. The result shown that juglone inhibited the growth of LNCaP cells in a dose-dependent manner. Morphological changes of apoptotic body formation after juglone treatment were observed by Hoechst 33342 staining. This apoptotic induction was associated with loss of mitochondrial membrane potential, and caspase-3, -9 activation. Moreover, we found that juglone significantly inhibited the expression levels of androgen receptor (AR) and prostate-specific antigen (PSA) in a dose-dependent manner, as well as abrogated up-regulation of AR and PSA genes with and/or without dihydrotestosterone (DHT). Take together, our results demonstrated that juglone might induce the apoptosis in LNCaP cell via down-regulation of AR expression. Therefore, our results indicated that juglone may be a potential candidate of drug for androgen-sensitive prostate cancer.

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[340]

**TÍTULO / TITLE:** - Differential regulation of cyclin-dependent kinase inhibitors in neuroblastoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 31;435(2):295-9. doi: 10.1016/j.bbrc.2013.04.023. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.04.023](#)

**AUTORES / AUTHORS:** - Qiao L; Paul P; Lee S; Qiao J; Wang Y; Chung DH

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, USA; Department of Pharmaceutical Sciences, Jilin University, Changchun 130021, PR China.

**RESUMEN / SUMMARY:** - Gastrin-releasing peptide (GRP) and its receptor (GRP-R) are highly expressed in undifferentiated neuroblastoma, and they play critical roles in oncogenesis. We previously reported that GRP activates the PI3K/AKT signaling pathway to promote DNA synthesis and cell cycle progression in neuroblastoma cells. Conversely, GRP-R silencing induces cell cycle arrest. Here, we speculated that GRP/GRP-R signaling induces neuroblastoma cell proliferation via regulation of cyclin-dependent kinase (CDK) inhibitors. Surprisingly, we found that GRP/GRP-R differentially induced expressions of p21 and p27. Silencing GRP/GRP-R decreased p21, but it increased p27 expressions in neuroblastoma cells. Furthermore, we found that the intracellular localization of p21 and p27 in the nuclear and cytoplasmic compartments, respectively. In addition, we found that GRP/GRP-R silencing increased the expression and accumulation of PTEN in the cytoplasm of neuroblastoma cells where it co-localized with p27, thus suggesting that p27 promotes the function of PTEN as a tumor suppressor by stabilizing PTEN in the cytoplasm. GRP/GRP-R regulation of CDK inhibitors and tumor suppressor PTEN may be critical for tumorigenesis of neuroblastoma.

[341]

**TÍTULO / TITLE:** - Epigallocatechin-3-gallate promotes apoptosis and expression of the caspase 9a splice variant in PC3 prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):194-200. doi: 10.3892/ijo.2013.1920. Epub 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1920](#)

**AUTORES / AUTHORS:** - Hagen RM; Chedea VS; Mintoff CP; Bowler E; Morse HR; Ladomery MR

**INSTITUCIÓN / INSTITUTION:** - Centre for Research in Bioscience, Faculty of Health and Life Sciences, University of the West of England, Coldharbour Lane, Frenchay, Bristol BS16 1QY, UK.

**RESUMEN / SUMMARY:** - Growing evidence suggests that the flavonoid epigallocatechin-3-gallate (EGCG), notably abundant in green tea, has health-promoting properties. We examined the effect of EGCG on cell survival and apoptosis in the prostate cancer cell line PC3. Cell survival was reduced and apoptosis increased significantly with a low dose of 1 microM EGCG. The ability

of the anticancer drug cisplatin to promote apoptosis was enhanced by EGCG. Furthermore, EGCG, both alone and in combination with cisplatin, promoted the expression of the pro-apoptotic splice isoform of caspase 9.

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[342]

**TÍTULO / TITLE:** - Synergistic induction of TRAIL-mediated apoptosis by anisomycin in human hepatoma cells via the BH3-only protein Bid and c-Jun/AP-1 signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 May;67(4):321-8. doi: 10.1016/j.biopha.2012.11.005. Epub 2012 Nov 23.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2012.11.005](#)

**AUTORES / AUTHORS:** - Jin CY; Park C; Hong SH; Han MH; Jeong JW; Xu H; Liu H; Kim GY; Kim WJ; Yoo YH; Choi YH

**INSTITUCIÓN / INSTITUTION:** - School of Pharmaceutical Science, Zhengzhou University, 100 Kexue Avenue, Zhengzhou, Henan 450001, China.

**RESUMEN / SUMMARY:** - Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF super-family, and it has been shown that many human cancer cell lines are refractory to TRAIL-induced cell death. However, the molecular mechanisms underlying resistance are unclear. In the present study, we show that TRAIL-resistance is reversed in human hepatoma cells by anisomycin, which is known to inhibit protein synthesis and induce ribotoxic stress. Synergistic induction of apoptosis in cells treated with anisomycin plus TRAIL was associated with activation of caspases and cleavage of Bid, a pro-apoptotic BH3-only protein. Silencing of Bid expression by small interfering RNA (siRNA) significantly attenuated the loss of mitochondrial membrane potential (MMP, Deltapsim) and significantly increased induction of apoptosis in cells treated with anisomycin and TRAIL, confirming that Bid cleavage is required for the response. In addition, c-Jun/AP-1 was rapidly activated upon stimulation with anisomycin; however, the knockdown of c-Jun/AP-1 expression by c-Jun siRNA markedly reduced anisomycin plus TRAIL-induced loss of MMP and apoptosis. Taken together, the findings show that anisomycin sensitizes TRAIL-mediated hepatoma cell apoptosis via the mitochondria-associated pathway, involving the cleavage of Bid and activation of the c-Jun/AP-1 pathway, indicating that this compound can be used as an anti-tumor agent in combination with TRAIL.

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[343]

**TÍTULO / TITLE:** - Mitochondrial energetic and AKT status mediate metabolic effects and apoptosis of metformin in human leukemic cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leukemia. 2013 Apr 9. doi: 10.1038/leu.2013.107.

●●Enlace al texto completo (gratis o de pago) [1038/leu.2013.107](https://doi.org/10.1038/leu.2013.107)

**AUTORES / AUTHORS:** - Scotland S; Saland E; Skuli N; de Toni F; Boutzen H; Micklow E; Senegas I; Peyraud R; Peyriga L; Theodoro F; Dumon E; Martineau Y; Danet-Desnoyers G; Bono F; Rocher C; Levade T; Manenti S; Junot C; Portais JC; Alet N; Recher C; Selak MA; Carroll M; Sarry JE

**INSTITUCIÓN / INSTITUTION:** - 1] INSERM, U1037, Cancer Research Center of Toulouse, CHU Purpan, Toulouse, France [2] Universite de Paul Sabatier, Toulouse III, Toulouse, France.

**RESUMEN / SUMMARY:** - Previous reports demonstrate that metformin, an anti-diabetic drug, can decrease the risk of cancer and inhibit cancer cell growth. However, its mechanism in cancer cells is still unknown. Metformin significantly blocks cell cycle and inhibits cell proliferation and colony formation of leukemic cells. However, the apoptotic response to metformin varies. Furthermore, daily treatment with metformin induces apoptosis and reduces tumor growth in vivo. While metformin induces early and transient activation of AMPK, inhibition of AMPK $\alpha$ 1/2 does not abrogate anti-proliferative or pro-apoptotic effects of metformin. Metformin decreases electron transport chain complex I activity, oxygen consumption and mitochondrial ATP synthesis, while stimulating glycolysis for ATP and lactate production, pentose phosphate pathway for purine biosynthesis, fatty acid metabolism, as well as anaplerotic and mitochondrial gene expression. Importantly, leukemic cells with high basal AKT phosphorylation, glucose consumption or glycolysis exhibit a markedly reduced induction of the Pasteur effect in response to metformin and are resistant to metformin-induced apoptosis. Accordingly, glucose starvation or treatment with deoxyglucose or an AKT inhibitor induces sensitivity to metformin. Overall, metformin elicits reprogramming of intermediary metabolism leading to inhibition of cell proliferation in all leukemic cells and apoptosis only in leukemic cells responding to metformin with AKT phosphorylation and a strong Pasteur effect. Leukemia (2013) advance online publication, 30 April 2013; doi:10.1038/leu.2013.107.

[344]

**TÍTULO / TITLE:** - Combination of fenretinide and indole-3-carbinol results in synergistic cytotoxic activity inducing apoptosis against human breast cancer cells in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Jul;24(6):577-86. doi: 10.1097/CAD.0b013e328360a921.

●●Enlace al texto completo (gratis o de pago)

[1097/CAD.0b013e328360a921](https://doi.org/10.1097/CAD.0b013e328360a921)

**AUTORES / AUTHORS:** - Cevatemre B; Ari F; Sarimahmut M; Oral AY; Dere E; Kacar O; Adiguzel Z; Acilan C; Ulukaya E

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Biology, Faculty of Arts and Sciences bDepartment of Medical Biochemistry, Medical School, Uludag University, Bursa cTUBITAK Marmara Research Center, Genetic Engineering and Biotechnology Institute, Kocaeli, Turkey.

**RESUMEN / SUMMARY:** - The outcome in patients with breast cancer is not satisfactory to date, although new chemotherapy regimens have been introduced in clinics. Therefore, novel approaches are required for better management of patients with breast cancer. In this study, we tested the cytotoxic activity of a new combination of fenretinide, a synthetic retinoid, with indole-3-carbinol, a natural product present in vegetables such as broccoli and cabbage, against MCF-7 (estrogen receptor-positive) and MDA-MB-231 (estrogen receptor-negative) cell lines. It has been found that the combination resulted in more powerful cytotoxic activity, by induction of apoptosis, compared with that when they were used singly. In conclusion, this novel combination warrants in-vivo experiments to elucidate its possible use in the treatment of breast cancer.

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[345]

**TÍTULO / TITLE:** - Nuclear expression of Smad proteins and its prognostic significance in clear cell renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Pathol. 2013 May 10. pii: S0046-8177(13)00133-0. doi: 10.1016/j.humpath.2013.03.009.

●●Enlace al texto completo (gratis o de pago)

[1016/j.humpath.2013.03.009](http://1016/j.humpath.2013.03.009)

**AUTORES / AUTHORS:** - Park JH; Lee C; Suh JH; Chae JY; Moon KC

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Seoul National University College of Medicine, Seoul 110-799, South Korea.

**RESUMEN / SUMMARY:** - Smad2, Smad3, and Smad4 are components of the transforming growth factor beta signaling pathway associated with tumorigenesis. The expression of these proteins is associated with tumor progression and prognosis of many cancers. This study aimed to evaluate the nuclear expression of Smad2, Smad3, and Smad4 in clear cell renal cell carcinoma and to assess the clinical significance and prognostic value of their expression patterns. The nuclear expression levels of Smads were evaluated in 637 cases of clear cell renal cell carcinomas using immunohistochemistry. To determine the statistical significance of Smad expression in clear cell renal cell carcinoma, each of the cases were divided into 2 groups (low and high expression groups) according to the extent of nuclear staining. Nuclear expressions of Smad3 and Smad4 were inversely correlated with the patient's age, the nuclear grade, the tumor size, and the pTNM stage. The Smad3-low and Smad4-low groups showed significantly shorter cancer-specific and progression-free survival times. Furthermore, multivariate analysis showed that

both Smad3 and Smad4 were independent predictors for progression-free survival ( $P = .008$  and  $P = .022$ , respectively). However, Smad2 expression was not related to clinicopathologic parameters and patients' survival. These results suggest that nuclear expressions of Smad3 and Smad4 were related to prognosis of clear cell renal cell carcinoma patients and may serve as novel prognostic markers in clear cell renal cell carcinoma patients.

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[346]

**TÍTULO / TITLE:** - Zebularine inhibits the growth of A549 lung cancer cells via cell cycle arrest and apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 May 9. doi: 10.1002/mc.22042.

●●Enlace al texto completo (gratis o de pago) [1002/mc.22042](#)

**AUTORES / AUTHORS:** - You BR; Park WH

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, Republic of Korea.

**RESUMEN / SUMMARY:** - Zebularine (Zeb) is a DNA methyltransferase (DNMT) inhibitor that has an anti-tumor effect. Here, we evaluated the anti-growth effect of Zeb on A549 lung cancer cells in relation to reactive oxygen species (ROS) levels. Zeb inhibited the growth of A549 cells with an IC50 of approximately 70  $\mu\text{M}$  at 72 h. Cell cycle analysis indicated that Zeb induced an S phase arrest in A549 cells. Zeb also induced A549 cell death, which was accompanied by the loss of mitochondrial membrane potential (MMP;  $\Delta\psi$ ), Bcl-2 decrease, Bax increase, p53 increase and activation of caspase-3 and -8. In contrast, Zeb mildly inhibited the growth of human pulmonary fibroblast (HPF) normal cells and led to a G1 phase arrest. Zeb did not induce apoptosis in HPF cells. In relation to ROS level, Zeb increased ROS level in A549 cells and induced glutathione (GSH) depletion. The well-known antioxidant, N-acetyl cysteine (NAC) prevented the death of Zeb-treated A549 cells. Moreover, Zeb increased the level of thioredoxin reductase 1 (TrxR1) in A549 cells. While the overexpression of TrxR1 attenuated death and ROS level in Zeb-treated A549 cells, the downregulation of TrxR1 intensified death and ROS level in these cells. In conclusion, Zeb inhibited the growth of A549 lung cancer cells via cell cycle arrest and apoptosis. The inhibition was influenced by ROS and TrxR1 levels. © 2013 Wiley Periodicals, Inc.

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[347]

**TÍTULO / TITLE:** - DNA methylation and histone modifications of Wnt genes by genistein during colon cancer development.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 24.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bqt129](http://1093/carcin/bqt129)

**AUTORES / AUTHORS:** - Zhang Y; Li Q; Chen H

**INSTITUCIÓN / INSTITUTION:** - Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA.

**RESUMEN / SUMMARY:** - This study aims to elucidate the epigenetic mechanisms by which genistein (GEN) maintains a normal level of WNT genes during colon cancer development. We have reported that soy protein isolate (SPI) and GEN repressed WNT signaling, correlating with the reduction of pre-neoplastic lesions in rat colon. We hypothesized that SPI and GEN induced epigenetic modifications on Sfrp2, Sfrp5 and Wnt5a genes, suppressing their gene expression induced by azoxymethane (AOM), a chemical carcinogen, to the similar level as that of pre-AOM period. We identified that in the post-AOM period, histone H3 acetylation (H3Ac) was downregulated by SPI and GEN at the promoter region of Sfrp2, Sfrp5 and Wnt5a, which paralleled with the reduced binding of RNA polymerase II. Nuclear level of histone deacetylase 3 was enhanced by SPI and GEN. The diets suppressed the trimethylation of histone H3 Lysine 9 (H3K9Me3) and the phosphorylation of histone H3 Serine 10 (H3S10P). Methylation of the specific region of Sfrp2, Sfrp5 and Wnt5a genes was increased by SPI and GEN, which was inversely correlated with the reduction of gene expression. Bisulfite sequencing further confirmed that dietary GEN induced DNA methylation at CpG island of the promoter region of Sfrp5. Importantly, this region includes a fragment that had decreased H3Ac. Here, we present a potential epigenetic mechanism by which dietary GEN controls the responses of WNT genes during carcinogen induction, which involves DNA methylation, histone modifications and their interactions at the regulatory region of gene.

[348]

**TÍTULO / TITLE:** - Prolonged hypocalcemia following denosumab therapy in metastatic hormone refractory prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bone. 2013 Apr 25;55(2):305-308. doi: 10.1016/j.bone.2013.04.012.

●●Enlace al texto completo (gratis o de pago) [1016/j.bone.2013.04.012](http://1016/j.bone.2013.04.012)

**AUTORES / AUTHORS:** - Milat F; Goh S; Gani LU; Suriadi C; Gillespie MT; Fuller PJ; Teede HJ; Strickland AH; Allan CA

**INSTITUCIÓN / INSTITUTION:** - Department of Endocrinology, Monash Health, Monash Medical Centre, Clayton, Australia; Bone Joint and Cancer Unit, Prince Henry's Institute, Block E, Level 4, Monash Medical Centre, Clayton, Australia; Department of Medicine, Southern Clinical School, Monash University, Clayton, Australia. Electronic address: [fran.milat@princehenrys.org](mailto:fran.milat@princehenrys.org).

**RESUMEN / SUMMARY:** - Prostate cancer is a leading cause of cancer death, frequently associated with widespread bone metastases. We report two cases

of hypocalcemia following the first dose of denosumab in metastatic hormone refractory prostate cancer, the first case requiring 26 days of intravenous calcium therapy. This is the first report of prolonged hypocalcemia following denosumab in a patient with normal renal function.

[349]

**TÍTULO / TITLE:** - Intracellular ATP-Binding Cassette Transporter A3 is Expressed in Lung Cancer Cells and Modulates Susceptibility to Cisplatin and Paclitaxel.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncology. 2013 May 15;84(6):362-370.

●●Enlace al texto completo (gratis o de pago) [1159/000348884](http://1159/000348884)

**AUTORES / AUTHORS:** - Overbeck TR; Hupfeld T; Krause D; Waldmann-Beushausen R; Chapuy B; Guldenzoph B; Aung T; Inagaki N; Schondube FA; Danner BC; Truemper L; Wulf GG

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Oncology, University Medical Center Gottingen, Gottingen, Germany.

**RESUMEN / SUMMARY:** - Patients with advanced-stage bronchial cancer benefit from systemic cytostatic therapy, in particular from regimens integrating cisplatin and taxanes. However, eventual disease progression leads to a fatal outcome in most cases, originating from tumor cells resisting chemotherapy. We here show that the intracellular ATP-binding cassette transporter A3 (ABCA3), previously recognized as critical for the secretion of surfactant components from type 2 pneumocytes, is expressed in non-small-cell lung cancer (NSCLC) cells. With some heterogeneity in a given specimen, expression levels detected immunohistochemically in primary cancer tissue were highest in adenocarcinomas and lowest in small cell lung cancers. Genetic silencing of ABCA3 in the NSCLC cell line models A549, NCI-H1650 and NCI-H1975 significantly increased tumor cell susceptibility to the cytostatic effects of both cisplatin (in all cell lines) and paclitaxel (in two of three cell lines). Taken together, ABCA3 emerges as a modulator of NSCLC cell susceptibility to cytostatic therapy.

[350]

**TÍTULO / TITLE:** - Targeting cell cycle and hormone receptor pathways in cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncogene. 2013 May 27. doi: 10.1038/onc.2013.83.

●●Enlace al texto completo (gratis o de pago) [1038/onc.2013.83](http://1038/onc.2013.83)

**AUTORES / AUTHORS:** - Comstock CE; Augello MA; Goodwin JF; de Leeuw R; Schiewer MJ; Ostrander WF Jr; Burkhart RA; McClendon AK; McCue PA; Trabulsi EJ; Lallas CD; Gomella LG; Centenera MM; Brody JR; Butler LM; Tilley WD; Knudsen KE

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA.

**RESUMEN / SUMMARY:** - The cyclin/cyclin-dependent kinase (CDK)/retinoblastoma (RB)-axis is a critical modulator of cell cycle entry and is aberrant in many human cancers. New nodes of therapeutic intervention are needed that can delay or combat the onset of malignancies. The antitumor properties and mechanistic functions of PD-0332991 (PD; a potent and selective CDK4/6 inhibitor) were investigated using human prostate cancer (PCa) models and primary tumors. PD significantly impaired the capacity of PCa cells to proliferate by promoting a robust G1-arrest. Accordingly, key regulators of the G1-S cell cycle transition were modulated including G1 cyclins D, E and A. Subsequent investigation demonstrated the ability of PD to function in the presence of existing hormone-based regimens and to cooperate with ionizing radiation to further suppress cellular growth. Importantly, it was determined that PD is a critical mediator of PD action. The anti-proliferative impact of CDK4/6 inhibition was revealed through reduced proliferation and delayed growth using PCa cell xenografts. Finally, first-in-field effects of PD on proliferation were observed in primary human prostatectomy tumor tissue explants. This study shows that selective CDK4/6 inhibition, using PD either as a single-agent or in combination, hinders key proliferative pathways necessary for disease progression and that RB status is a critical prognostic determinant for therapeutic efficacy. Combined, these pre-clinical findings identify selective targeting of CDK4/6 as a bona fide therapeutic target in both early stage and advanced PCa and underscore the benefit of personalized medicine to enhance treatment response. Oncogene advance online publication, 27 May 2013; doi:10.1038/onc.2013.83.

[351]

**TÍTULO / TITLE:** - Pharmacogenomics of endocrine therapy in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hum Genet. 2013 May 2. doi: 10.1038/jhg.2013.35.

●●Enlace al texto completo (gratis o de pago) [1038/jhg.2013.35](#)

**AUTORES / AUTHORS:** - Ingle JN

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA.

**RESUMEN / SUMMARY:** - The most important modality of treatment in the two-thirds of patients with an estrogen receptor (ER)-positive early breast cancer is endocrine therapy. In postmenopausal women, options include the selective ER modulators (SERMs), tamoxifen and raloxifene, and the 'third-generation' aromatase inhibitors (AIs), anastrozole, exemestane and letrozole. Under the auspices of the National Institutes of Health Global Alliance for Pharmacogenomics, Japan, the Mayo Clinic Pharmacogenomics Research Network Center and the RIKEN Center for Genomic Medicine have worked

collaboratively to perform genome-wide association studies (GWAS) in women treated with both SERMs and AIs. On the basis of the results of the GWAS, scientists at the Mayo Clinic have proceeded with functional genomic laboratory studies. As will be seen in this review, this has led to new knowledge relating to endocrine biology that has provided a clear focus for further research to move toward truly personalized medicine for women with breast cancer. *Journal of Human Genetics* advance online publication, 2 May 2013; doi:10.1038/jhg.2013.35.

[352]

**TÍTULO / TITLE:** - MiR-365b-3p, down-regulated in retinoblastoma, regulates cell cycle progression and apoptosis of human retinoblastoma cells by targeting PAX6.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *FEBS Lett.* 2013 May 6. pii: S0014-5793(13)00324-4. doi: 10.1016/j.febslet.2013.04.029.

●●Enlace al texto completo (gratis o de pago)

[1016/j.febslet.2013.04.029](http://1016/j.febslet.2013.04.029)

**AUTORES / AUTHORS:** - Wang J; Wang X; Wu G; Hou D; Hu Q

**INSTITUCIÓN / INSTITUTION:** - Eye Hospital, The First Affiliated Hospital, Harbin Medical University, No. 23 You Zheng Road, Harbin 150001, China.

**RESUMEN / SUMMARY:** - PAX6 contributes to the development and progression of retinoblastoma (RB), but the molecular mechanism underlying the regulation of PAX6 expression is unclear. Here we found that microRNA-365b-3p (miR-365b-3p) is downregulated in human RB tissues. Ectopic expression of miR-365b-3p significantly attenuates cell growth, induces cell cycle arrest in G1 phase and cell apoptosis through inhibiting the expression of PAX6 by directly binding its 3' untranslated regions. Furthermore, overexpression of miR-365b-3p upregulates p21 and p27 but downregulates cdc2 and Cyclin D1 protein levels. Elucidating the regulatory mechanism of PAX6 by microRNAs may give new clues to the therapy against RB.

[353]

**TÍTULO / TITLE:** - A phase 1b study of trametinib, an oral Mitogen-activated protein kinase kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Eur J Cancer.* 2013 Apr 11. pii: S0959-8049(13)00223-2. doi: 10.1016/j.ejca.2013.03.020.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.03.020](http://1016/j.ejca.2013.03.020)

**AUTORES / AUTHORS:** - Infante JR; Papadopoulos KP; Bendell JC; Patnaik A; Burris HA 3rd; Rasco D; Jones SF; Smith L; Cox DS; Durante M; Bellew KM; Park JJ; Le NT; Tolcher AW

**INSTITUCIÓN / INSTITUTION:** - Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA. Electronic address: [jinfante@tnonc.com](mailto:jinfante@tnonc.com).

**RESUMEN / SUMMARY:** - PURPOSE: This phase 1b study determined the safety, tolerability, and recommended phase 2 dose (RP2D) and schedule of trametinib in combination with gemcitabine. Secondary objectives included assessment of clinical activity and steady-state pharmacokinetics. METHODS: Adults with advanced solid tumours, adequate organ function and Eastern Co-operative Oncology Group performance status (ECOG PS)1 were eligible. Once-daily oral trametinib (1mg, 2mg, 2.5mg) was escalated in a 3+3 design with standard gemcitabine dosing (1000mg/m<sup>2</sup> IV Days 1, 8, and 15 of 28-day cycles). During expansion, trametinib 2mg was combined with gemcitabine. Pharmacokinetics samples were collected on Day 15 pre-dose and 1, 2, 4 and 6h post-dose; tumour assessments were repeated every two cycles. RESULTS: Between 8/2009 and 11/2010, 31 patients (pancreas=11, breast=6, non-small cell lung cancer (NSCLC)=4, other=10) were treated. Dose-limiting toxicities (DLTs) occurred in each cohort, and included febrile neutropenia, transaminase elevation and uveitis. The RP2D was declared as trametinib 2mg daily with standard gemcitabine dosing. Common grade  $\geq$ 4 toxicities at the RP2D included: neutropenia (38%), thrombocytopenia (19%) and transaminase elevation (14%). Of 10 patients with measurable pancreatic cancer, three partial responses (30%) were documented; two additional patients achieved objective responses (breast, complete response (CR); salivary glands, partial response (PR)). Pharmacokinetics suggested no change in exposures of either drug in combination. CONCLUSION: Administration of trametinib at its full monotherapy dose of 2mg daily in combination with standard gemcitabine dosing (1000mg/m<sup>2</sup> IV Days 1, 8, and 15 every 28 days) was feasible. Though most toxicities were manageable, the addition of trametinib may increase gemcitabine-associated myelosuppression. Future studies of this combination will require monitoring to maintain dose and schedule.

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[354]

**TÍTULO / TITLE:** - Salinomycin induces apoptosis via death receptor-5 up-regulation in cisplatin-resistant ovarian cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1457-62.

**AUTORES / AUTHORS:** - Parajuli B; Shin SJ; Kwon SH; Cha SD; Chung R; Park WJ; Lee HG; Cho CH

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Keimyung University School of Medicine, Daegu, Republic of Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Chemo-resistance to cisplatin-centered cancer therapy is a major obstacle to effective disease treatment. Recently, salinomycin was proven to be highly-effective for the elimination of cancer stem cells both in vitro and in vivo. The objective of the present study was to evaluate the anticancer properties of salinomycin in cisplatin-resistant ovarian cancer cells (A2780cis). MATERIALS AND METHODS: The tetrazolium dye (MTT) assay was used to determine cell viability. Flow cytometric analysis was performed to analyze the effect on cell cycle and apoptosis. The expression of apoptosis-related proteins was evaluated by western blot analysis. RESULTS: Cell viability was significantly reduced by salinomycin treatment in a dose-dependent manner. Flow cytometry showed an increase in sub-G1 phase cells. Salinomycin increased the expression of death receptor-5 (DR5), caspase-8 and Fas-associated protein with death domain (FADD). A decline in the expression of FLICE-like inhibitory protein (FLIP), activation of caspase-3 and increased poly ADP-ribose polymerase (PARP) cleavage, triggered apoptosis. Furthermore, annexin-V staining also revealed the apoptotic induction. CONCLUSION: These findings provide important insights regarding the activation of caspase-8 and DR5, to our knowledge, for the first time in salinomycin-treated cisplatin-resistant ovarian cancer and demonstrate that salinomycin could be a prominent anticancer agent.

[355]

**TÍTULO / TITLE:** - Monocyte chemotactic protein-1 and CC chemokine receptor 2 polymorphisms and prognosis of renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0827-](#)

[7](#)

**AUTORES / AUTHORS:** - Liu GX; Zhang X; Li S; Koiiche RD; Sindsceii JH; Song H

**INSTITUCIÓN / INSTITUTION:** - Department of Nephrology, Huizhou Municipal Central Hospital, 41 E Ling Bei Road, Huizhou, Guangdong, 516001, China, [quanxian\\_liu@126.com](mailto:quanxian_liu@126.com).

**RESUMEN / SUMMARY:** - Monocyte chemoattractant protein-1 (MCP-1) and its receptor CC chemokine receptor 2 (CCR2) play a major role in inflammation and proliferation of cancers. We investigated a possible association between polymorphisms in MCP-1 and CCR2 genes (MCP-1 -2518A/G and CCR2 190G/A or V64I) and the risk as well as prognosis of renal cell carcinoma (RCC). Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism in 416 RCC cases and 458 age-matched healthy controls. Frequency of MCP-1 2518GG genotype for cases and controls was 0.384 and 0.286, respectively; individuals carrying the GG genotype had a 1.89-fold increased risk of RCC than those with AA genotype (95 % confidence

interval [CI] 1.24-2.81,  $p = 0.002$ ; data were adjusted for age and sex). Frequency of CCR2 190AA (64I/64I) genotype for cases and controls was 0.175 and 0.076, respectively; subjects having AA genotype had a 2.68-fold increased risk of RCC compared to those with the wild-type GG genotype (95 %CI 1.71-4.17,  $p = 4.3 \times 10^{-6}$ ; data were adjusted for age and sex). When analyzing the survival rate of RCC, patients with MCP-1 -2518GG genotype revealed significantly shorter survival time compared to cases with MCP-1 -2518AA and AG genotypes ( $p = 0.003$ ). Similarly, RCC cases carrying CCR2 190AA genotype showed significantly shorter survival rate than patients with GG or GA genotypes ( $p < 0.001$ ). These data suggested that MCP-1 -2518A/G and CCR2 190G/A polymorphisms are new risk factors for RCC and could be used as prognostic markers for this malignancy.

[356]

**TÍTULO / TITLE:** - miR-138 overexpression is more powerful than hTERT knockdown to potentiate apigenin for apoptosis in neuroblastoma in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Cell Res. 2013 Jun 10;319(10):1575-85. doi: 10.1016/j.yexcr.2013.02.025. Epub 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago)

[1016/j.yexcr.2013.02.025](#)

**AUTORES / AUTHORS:** - Chakrabarti M; Banik NL; Ray SK

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, SC, USA.

**RESUMEN / SUMMARY:** - Decrease in expression of the tumor suppressor microRNA-138 (miR-138) correlates well with an increase in telomerase activity in many human cancers. The ability of almost all human cancer cells to grow indefinitely is dependent on presence of telomerase activity. The catalytic component of human telomerase reverse transcriptase (hTERT) regulates telomerase activity in most of the human cancers including malignant neuroblastoma. We observed an indirect increase in the expression of miR-138 after the transfection with hTERT short hairpin RNA (shRNA) plasmid in human malignant neuroblastoma SK-N-DZ and SK-N-BE2 cell lines. Transfection with hTERT shRNA plasmid followed by treatment with the flavonoid apigenin (APG) further increased expression of miR-138. Direct transfection with miR-138 mimic was more powerful than transfection with hTERT shRNA plasmid in potentiating efficacy of APG for decreasing cell viability and colony formation capability of both cell lines. Upregulation of miR-138 was also more effective than down regulation of hTERT in enhancing efficacy of APG for induction of apoptosis in malignant neuroblastoma cells in vitro and in vivo. We delineated that apoptosis occurred with induction of molecular components of the extrinsic

and intrinsic pathways in SK-N-DZ and SK-N-BE2 cells both in vitro and in vivo. In conclusion, these results demonstrate that direct miR-138 overexpression is more powerful than hTERT down regulation in enhancing pro-apoptotic effect of APG for controlling growth of human malignant neuroblastoma in cell culture and animal models.

[357]

**TÍTULO / TITLE:** - The role of single nucleotide polymorphisms of the ERCC1 and MMS19 genes in predicting platinum-sensitivity, progression-free and overall survival in advanced epithelial ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Apr 28. pii: S0090-8258(13)00310-7. doi: 10.1016/j.ygyno.2013.04.054.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.04.054](#)

**AUTORES / AUTHORS:** - Moxley KM; Benbrook DM; Queimado L; Zuna RE; Thompson D; McCumber M; Premkumar P; Thavathiru E; Hines L; Moore KN

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, College of Public Health University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. Electronic address: [Katherine-moxley@ouhsc.edu](mailto:Katherine-moxley@ouhsc.edu).

**RESUMEN / SUMMARY:** - OBJECTIVE: This study aims to assess the role of polymorphisms in DNA repair genes, excision repair cross-complementation group 1 (ERCC1) and methyl-methanesulfonate sensitivity 19 (MMS19), in tumor response to platinum-based chemotherapy and survival in advanced epithelial ovarian cancer (EOC). METHODS: Single nucleotide polymorphism (SNP) analysis was performed on the paraffin-embedded tumor tissue of women with advanced EOC, treated with platinum-based chemotherapy at the University of Oklahoma Health Sciences Center. Polymorphisms from two ERCC1 (codon-118 and C8092A) and three MMS19 (rs2211243, rs2236575 and rs872106) gene loci were evaluated by real time PCR Allelic Discrimination Assay. RESULTS: Genotyping was performed in 107 patients, 45 platinum-sensitive and 62 platinum-resistant. ERCC1, codon-118 and C8092A genotyping was evaluable in 98 and 106 patients respectively and in all 107 patients for MMS19 polymorphisms. No differences were observed in genotype between platinum-sensitive and platinum-resistant patients. Polymorphisms in the ERCC1, codon-118 and MMS19 genes did not correlate with overall survival (OS), although a trend toward improved progression free survival (PFS) was observed in patients expressing the minor (GG) alleles of the rs872106 MMS19 gene. Women homozygous for the ERCC1-C8092A minor (AA) alleles had a significant increase in PFS compared to AC and CC patients and both AA and AC genotypes conferred improved survival over the major (CC) genotype. CONCLUSIONS: Polymorphisms in ERCC1, codon-118 and MMS19 genes are not associated with clinical response to platinum or survival. The

ERCC1-C8092A genotypes containing an "A" allele were associated with significant improvement in PFS and OS strengthening the value of this specific genotype in survival.

[358]

**TÍTULO / TITLE:** - The occurrence of second neoplasms after treatment with tyrosine kinase inhibitors for chronic myeloid leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 23.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.806805](#)

**AUTORES / AUTHORS:** - Togasaki-Yoshimoto E; Shono K; Onoda M; Yokota A

[359]

**TÍTULO / TITLE:** - Differential Effects of Dehydroepiandrosterone and Testosterone in Prostate and Colon Cancer Cell Apoptosis: The Role of Nerve Growth Factor (NGF) Receptors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Endocrinology. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1210/en.2012-2249](#)

**AUTORES / AUTHORS:** - Anagnostopoulou V; Pediaditakis I; Alkahtani S; Alarifi SA; Schmidt EM; Lang F; Gravanis A; Charalampopoulos I; Stournaras C

**INSTITUCIÓN / INSTITUTION:** - Departments of Biochemistry (V.A., C.S.) and Pharmacology (I.P., A.G., I.C.), University of Crete Medical School, GR-71003 Heraklion, Greece; Foundation of Research and Technology (IESL-FORTH) (I.P., A.G.), Heraklion, Greece; Department of Zoology (S.A., S.A.A.), Science College, King Saud University, Riyadh, Saudi Arabia; and Department of Physiology (E.-M.S., F.L., C.S.), University of Tübingen, Tübingen, Germany.

**RESUMEN / SUMMARY:** - Tumor growth is fostered by inhibition of cell death, which involves the receptiveness of tumor to growth factors and hormones. We have recently shown that testosterone exerts proapoptotic effects in prostate and colon cancer cells through a membrane-initiated mechanism. In addition, we have recently reported that dehydroepiandrosterone (DHEA) can control cell fate, activating nerve growth factor (NGF) receptors, namely tropomyosin-related kinase (Trk)A and p75NTR, in primary neurons and in PC12 tumoral cells. NGF was recently involved in cancer cell proliferation and apoptosis. In the present study, we explored the cross talk between androgens (testosterone and DHEA) and NGF in regulating apoptosis of prostate and colon cancer cells. DHEA and NGF strongly blunted serum deprivation-induced apoptosis, whereas testosterone induced apoptosis of both cancer cell lines. The antiapoptotic effect of both DHEA and NGF was completely reversed by testosterone. In line with this, DHEA or NGF up-regulated, whereas testosterone down-regulated,

the expression of TrkA receptor. The effects of androgens were abolished in both cell lines in the presence of TrkA inhibitor. DHEA induced the phosphorylation of TrkA and the interaction of p75NTR receptor with its effectors, RhoGDI and RIP2. Conversely, testosterone was unable to activate both receptors. Testosterone acted as a DHEA and NGF antagonist, by blocking the activation of both receptors by DHEA or NGF. Our findings suggest that androgens may influence hormone-sensitive tumor cells via their cross talk with NGF receptors. The interplay between steroid hormone and neurotrophins signaling in hormone-dependent tumors offers new insights in the pathophysiology of these neoplasias.

[360]

**TÍTULO / TITLE:** - Thymidylate synthase gene copy number as a predictive marker for response to pemetrexed treatment of lung adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):1935-40.

**AUTORES / AUTHORS:** - Kasai D; Ozasa H; Oguri T; Miyazaki M; Uemura T; Takakuwa O; Kunii E; Ohkubo H; Maeno K; Niimi A

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. [t-oguri@med.nagoya-cu.ac.jp](mailto:t-oguri@med.nagoya-cu.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: Pemetrexed is a key drug for therapy of non-small cell lung cancer (NSCLC). MATERIALS AND METHODS: In a search for biomarkers for study of the efficacy of pemetrexed treatment, we examined the thymidylate synthase (TYMS) copy number in NSCLC cell lines and in clinical NSCLC samples treated with pemetrexed, combined with platinum drugs. RESULTS: TYMS copy numbers in lung adenocarcinoma cell lines were significantly lower than in squamous cell carcinoma ( $p=0.0105$ ), and a significant correlation was found between the TYMS copy number and the 50% inhibitory concentration value for pemetrexed in all 17 lung cancer cell lines tested ( $r=0.6814$ ,  $p=0.0026$ ). Moreover, TYMS copy number was significantly lower in clinical NSCLC samples responsive to treatment with pemetrexed combined with platinum drugs ( $p=0.0067$ ). Furthermore, the decrease in the baseline CT size measurement of pemetrexed combined with platinum drug treatment correlated significantly with TYMS copy number ( $r=0.7967$ ,  $p=0.0011$ ). CONCLUSION: To our knowledge, this is the first report of a significant association between TYMS copy number and response to pemetrexed treatment in tumor biopsy specimens. Our results suggest that TYMS copy number could be a predictive biomarker for pemetrexed based chemotherapy.

[361]

**TÍTULO / TITLE:** - Vinblastine-induced apoptosis of melanoma cells is mediated by Ras homologous A protein (Rho A) via mitochondrial and non-mitochondrial-dependent mechanisms.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Apoptosis. 2013 Apr 7.

●●Enlace al texto completo (gratis o de pago) [1007/s10495-013-0844-](#)

[4](#)

**AUTORES / AUTHORS:** - Selimovic D; Badura HE; El-Khattouti A; Soell M; Porzig BB; Spernger A; Ghanjati F; Santourlidis S; Haikel Y; Hassan M

**INSTITUCIÓN / INSTITUTION:** - Institut National de la Sante et de la Recherche Medicale, U 977, Faculty of Medicine and Dental Faculty, 11 Rue Humann, 67000, Strasbourg, France.

**RESUMEN / SUMMARY:** - Despite the availability of melanoma treatment at the primary site, the recurrence of local melanoma can metastasize to any distant organ. Currently, the available therapies for the treatment of metastatic melanoma are of limited benefit. Thus, the functional analysis of conventional therapies may help to improve their efficiency in the treatment of metastatic melanoma. In the present study, the exposure of melanoma cells to vinblastine was found to trigger apoptosis as evidenced by the loss of mitochondrial membrane potential, the release of both cytochrome c and apoptosis inducing factor, activation of caspase-9 and 3, and cleavage of Poly (ADP-ribose)-Polymerase. Also, vinblastine enhances the phosphorylation of Ras homologous protein A, the accumulation of reactive oxygen species, the release of intracellular Ca<sup>2+</sup>, as well as the activation of apoptosis signal-regulating kinase 1, c-jun-N-terminal kinase, p38, inhibitor of kappaB (IkappaB) kinase, and inositol requiring enzyme 1alpha. In addition, vinblastine induces the DNA-binding activities of the transcription factor NF-kappaB, HSF1, AP-1, and ATF-2, together with the expression of HSP70 and Bax proteins. Moreover, inhibitory experiments addressed a central role for Rho A in the regulation of vinblastine-induced apoptosis of melanoma cells via mitochondrial and non-mitochondrial-dependent mechanisms. In conclusion, the present study addresses for the first time a central role for Rho A in the modulation of vinblastine-induced apoptosis of melanoma cells and thereby provides an insight into the molecular action of vinblastine in melanoma treatment.

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[362]

**TÍTULO / TITLE:** - Disrupting Protein NEDDylation with MLN4924 is a Novel Strategy to Target Cisplatin Resistance in Ovarian Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3212](#)

**AUTORES / AUTHORS:** - Nawrocki ST; Kelly KR; Smith PG; Espitia CM; Possemato A; Beausoleil SA; Milhollen MA; Blakemore S; Thomas M; Berger AJ; Carew JS

**INSTITUCIÓN / INSTITUTION:** - Medicine, Institute for Drug Development CTCRC at UTHSCSA.

**RESUMEN / SUMMARY:** - **PURPOSE:** Ovarian cancer has the highest mortality rate of all female reproductive malignancies. Drug resistance is a major cause of treatment failure and novel therapeutic strategies are urgently needed. MLN4924 is a NEDDylation inhibitor currently under investigation in multiple Phase I studies. We investigated its anticancer activity in cisplatin sensitive (CS) and cisplatin resistant (CR) ovarian cancer models. **EXPERIMENTAL DESIGN:** Cellular sensitivity to MLN4924/cisplatin was determined by measuring viability, clonogenic survival, and apoptosis. The effects of drug treatment on global protein expression, DNA damage, and reactive oxygen species generation were determined. RNA interference established NBK/BIK as a regulator of therapeutic sensitivity. The in vivo effects of MLN4924/cisplatin on tumor burden and key pharmacodynamics endpoints were assessed in CS and CR xenograft models. **RESULTS:** MLN4924 possessed significant activity against both CS and CR ovarian cancer cells and provoked the stabilization of key NEDD8 substrates and regulators of cellular redox status. Notably, MLN4924 significantly augmented the activity of cisplatin against CR cells, suggesting that aberrant NEDDylation may contribute to drug resistance. MLN4924 and cisplatin cooperated to induce DNA damage, oxidative stress, and increased expression of the BH3-only protein NBK/BIK. Targeted NBK/BIK knockdown diminished the pro-apoptotic effects of the MLN4924/cisplatin combination. Administration of MLN4924 to mice bearing ovarian tumor xenografts significantly increased the efficacy of cisplatin against both CS and CR tumors. **CONCLUSIONS:** Our collective data provide a rationale for the clinical investigation of NAE inhibition as a novel strategy to augment cisplatin efficacy in patients with ovarian cancer and other malignancies.

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[363]

**TÍTULO / TITLE:** - Tau proteins expressions in advanced breast cancer and its significance in taxane-containing neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):591. doi: 10.1007/s12032-013-0591-y. Epub 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0591-](#)

[y](#)

**AUTORES / AUTHORS:** - Li ZH; Xiong QY; Tu JH; Gong Y; Qiu W; Zhang HQ; Wei WS; Hou YF; Cui WQ

**INSTITUCIÓN / INSTITUTION:** - Prevention and Cure Center of Breast Disease, The Third Hospital of Nanchang City, Nanchang, 330009, JiangXi, People's Republic of China, [huazhili0802@163.com](mailto:huazhili0802@163.com).

**RESUMEN / SUMMARY:** - Tau is a microtubule-associated protein and expressed in normal breast epithelial cells and breast cancer. Tau expression in breast cancer may be important for chemotherapy optimization. This study is to investigate the expression of Tau in advanced breast cancer and its significance in taxane-containing neoadjuvant chemotherapy. Levels of Tau protein in advanced breast cancer were detected immunohistochemically. The chemotherapeutic efficacy indexes in Tau(-) group, which includes the remission rate, Miller-Payne pathological reactive grade, and pathologic complete response rate, were improved compared with that in Tau(+) group. There was difference in the efficacy indexes among ER+ subgroups but not among ER- patients. In addition, Tau expression was positively correlated ( $r = 0.32$ ,  $P < 0.00$ ). In multivariate analysis, when age, clinical stage, postoperative lymph node metastasis, ER, PR, HER2, Ki-67, TP53, or Tau status were included, postoperative lymph node metastasis and Tau-negative status were identified as independent predictors of pathologic complete response. In conclusion, negative Tau protein expression may be an effective predictor for taxane-containing neoadjuvant chemotherapy, especially in ER+ subgroups. Further study on the molecular mechanism and utility of Tau for individualizing adjuvant chemotherapy is warranted.

[364]

**TÍTULO / TITLE:** - Transplatin enhances effect of cisplatin on both single DNA molecules and live tumor cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Biochem Biophys. 2013 May 8. pii: S0003-9861(13)00150-1. doi: 10.1016/j.abb.2013.04.014.

●●Enlace al texto completo (gratis o de pago) [1016/j.abb.2013.04.014](http://1016/j.abb.2013.04.014)

**AUTORES / AUTHORS:** - Liu YR; Ji C; Zhang HY; Dou SX; Xie P; Wang WC; Wang PY

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Soft Matter Physics, Beijing National Laboratory for Condensed Matter Physics, Institute of Physics, Chinese Academy of Sciences, Beijing 100190, China.

**RESUMEN / SUMMARY:** - Cisplatin is the main platinum antitumor drug applied in clinical settings. However, its trans isomer, transplatin, is known to have an ineffective antitumor activity. Despite intensive studies in this field, the structural and biophysical properties of DNA molecules reacting with these two platinum complexes have not been fully elucidated. In the present study, we observed that transplatin made efficient cross-linking of DNA in the vicinity of cisplatin adducts. High-resolution atomic force microscopy studies revealed that the transplatin-induced cross-linkings of nucleotides flanking cisplatin adducts were

characterized by kinked-loop structures with rod-like shapes of nanometer scales (approximately 10-60nm). The results were further confirmed by denaturing gel electrophoresis and single-molecule experiment using magnetic tweezers. In vivo studies revealed that transplatin and cisplatin co-treatment could induce a considerable amount of kinked loops with smaller sizes (approximately 15nm) in cellular DNA. Furthermore, compared with cisplatin treatment alone, the co-treatment resulted in enhanced cytotoxicity, increased amount of interstrand cross-links, and cell lesions more reluctant to cellular repair system. The results of the present study provide a new clue for understanding the stepwise reactions of DNA with platinum drugs and might serve as a basis for the development of a new antitumor strategy.

[365]

**TÍTULO / TITLE:** - An Insulin-like Growth Factor-II Intronic Variant Affects Local DNA Conformation and Ovarian Cancer Survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 14.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bqt168](#)

**AUTORES / AUTHORS:** - Lu L; Risch E; Deng Q; Biglia N; Picardo E; Katsaros D; Yu H

**INSTITUCIÓN / INSTITUTION:** - Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT 06520-8034, USA.

**RESUMEN / SUMMARY:** - Insulin-like growth factor-II (IGF-II) may be a prognostic marker in ovarian cancer, and its intronic SNP rs4320932 has been associated with risk of the disease. We determined whether rs4320932 is associated with IGF expression and patient survival in ovarian cancer, and explored whether the SNP variation affects DNA conformation both in the absence of and presence of carboplatin. IGF-II genotype (rs4320932) and phenotype were analyzed in 212 primary invasive epithelial ovarian cancer tissue samples with Taqman® SNP-genotyping assays, quantitative RT-PCR, and commercial ELISA. DNA conformation was evaluated by circular dichroism (CD) spectra. Kaplan-Meier survival curves and Cox proportional hazard regression models were used to analyze the SNP associations with patient survival. The C allele of rs4320932, previously associated with decreased risk of ovarian cancer development, was here associated with significantly elevated risks of relapse (ptrend=0.0002) and death (ptrend=0.0006), remaining significant in multivariate analyses. The adjusted hazard ratios were 3.09 (95% CI: 1.48-6.45) for relapse and 3.35 (95% CI: 1.68-6.71) for death, respectively. The variant was also significantly associated with chemotherapy response, but not with other clinicopathologic variables or with IGF-II expression. DNA with genotypes TT and CC had distinct CD spectra in both the absence of and presence of carboplatin. These findings suggest that the intronic SNP rs4320932 affects patient survival and chemotherapy response via alteration of DNA conformation, but not through

regulation of IGF-II expression. This novel finding may have implications in individualized medicine for the design of specific molecules targeting DNA of specific conformations.

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[366]

**TÍTULO / TITLE:** - Oestrogen receptor co-activator AIB1 is a marker of tamoxifen benefit in postmenopausal breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 May 12.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt159](#)

**AUTORES / AUTHORS:** - Weiner M; Skoog L; Fornander T; Nordenskjöld B; Sgroi DC; Stal O

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, County Council of Östergötland, Linköping.

**RESUMEN / SUMMARY:** - BACKGROUND: The oestrogen receptor (ER) co-activator amplified in breast cancer 1 (AIB1) has been suggested as a treatment predictive and prognostic marker in breast cancer. Studies have however not been unanimous. PATIENTS AND METHODS: AIB1 protein expression was analysed by immunohistochemistry on tissue micro-arrays with tumour samples from 910 postmenopausal women randomised to tamoxifen treatment or no adjuvant treatment. Associations between AIB1 expression, clinical outcome in the two arms and other clinicopathological variables were examined. RESULTS: In patients with ER-positive breast cancer expressing low tumour levels of AIB1 (<75%), we found no significant difference in recurrence-free survival (RFS) or breast cancer-specific survival (BCS) between tamoxifen treated and untreated patients. In patients with high AIB1 expression (>75%), there was a significant decrease in recurrence rate (HR 0.40, 95% CI 0.26-0.61, P < 0.001) and breast cancer mortality rate (HR 0.38, 95% CI 0.21-0.69, P = 0.0015) with tamoxifen treatment. In the untreated arm, we found high expression of AIB1 to be significantly associated with lower RFS (HR 1.74, 95% CI 1.20-2.53, P = 0.0038). CONCLUSION: Our results suggest that high AIB1 is a predictive marker of good response to tamoxifen treatment in postmenopausal women and a prognostic marker of decreased RFS in systemically untreated patients.

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[367]

**TÍTULO / TITLE:** - Ultrasound-targeted HSVtk and Timp3 gene delivery for synergistically enhanced antitumor effects in hepatoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Gene Ther. 2013 May;20(5):290-7. doi: 10.1038/cgt.2013.19. Epub 2013 Apr 19.

●●Enlace al texto completo (gratis o de pago) [1038/cgt.2013.19](#)

**AUTORES / AUTHORS:** - Yu BF; Wu J; Zhang Y; Sung HW; Xie J; Li RK  
**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Shanxi Medical University, Taiyuan, China.  
**RESUMEN / SUMMARY:** - Cancer gene therapy has great potential for decreasing tumor-induced mortality but has been clinically limited by non-targeted and insufficient gene transfer. We evaluated gene therapy targeting hepatocellular carcinoma (HCC) using the herpes simplex virus thymidine kinase/ganciclovir (HSVtk/GCV) suicide gene system and the tissue inhibitor of metalloproteinase 3 (Timp3) gene. Ultrasound-targeted microbubble destruction (UTMD) targeted gene delivery to the tumor tissue, and the alpha-fetoprotein promoter targeted HSVtk expression to the HCC cells. Human HepG2 cells transfected with the HSVtk or Timp3 gene demonstrated a reduction in cell viability by >40% compared with the vector control. Cell viability was further inhibited by over 50% with co-transfection of the genes. HepG2 cells were inoculated subcutaneously into athymic mice to induce tumors. UTMD-mediated delivery of HSVtk or Timp3 suppressed tumor growth by >45% and increased survival of tumor-bearing animals (P<0.01 vs vector control). Co-delivery of the genes resulted in a further 30% improvement in tumor suppression and significant extension of animal survival (P<0.01 vs vector control). Targeted gene delivery increased the number of apoptotic cells and decreased the vascular density of the tumors. Targeted co-delivery of the genes synergistically improved the antitumor effects and may provide an effective therapy for HCC.

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[368]

**TÍTULO / TITLE:** - mTOR inhibitors radiosensitize PTEN-deficient non-small-cell lung cancer cells harboring an EGFR activating mutation by inducing autophagy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 Jun;114(6):1248-56. doi: 10.1002/jcb.24465.

●●Enlace al texto completo (gratis o de pago) [1002/jcb.24465](#)

**AUTORES / AUTHORS:** - Kim EJ; Jeong JH; Bae S; Kang S; Kim CH; Lim YB  
**INSTITUCIÓN / INSTITUTION:** - Division of Radiation Effects, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Republic of Korea.

**RESUMEN / SUMMARY:** - Clinical resistance to gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), in patients with lung cancer has been linked to acquisition of the T790M resistance mutation in activated EGFR or amplification of MET. Phosphatase and tensin homolog (PTEN) loss has been recently reported as a gefitinib resistance mechanism in lung cancer. The aim of this study was to evaluate the efficacy of radiotherapy in non-small-cell lung cancer (NSCLC) with acquired gefitinib resistance caused by PTEN deficiency to suggest radiotherapy as an alternative to EGFR TKIs. PTEN deficient-mediated gefitinib resistance was generated in HCC827

cells, an EGFR TKI sensitive NSCLC cell line, by PTEN knockdown with a lentiviral vector expressing short hairpin RNA-targeting PTEN. The impact of PTEN knockdown on sensitivity to radiation in the presence or absence of PTEN downstream signaling inhibitors was investigated. PTEN knockdown conferred acquired resistance not only to gefitinib but also to radiation on HCC827 cells. mTOR inhibitors alone failed to reduce HCC827 cell viability, regardless of PTEN expression, but ameliorated PTEN knockdown-induced radioresistance. PTEN knockdown-mediated radioresistance was accompanied by repression of radiation-induced cytotoxic autophagy, and treatment with mTOR inhibitors released the repression of cytotoxic autophagy to overcome PTEN knockdown-induced radioresistance in HCC827 cells. These results suggest that inhibiting mTOR signaling could be an effective strategy to radiosensitize NSCLC harboring the EGFR activating mutation that acquires resistance to both TKIs and radiotherapy due to PTEN loss or inactivation mutations.

[369]

**TÍTULO / TITLE:** - Histone deacetylase inhibitor AR42 regulates telomerase activity in human glioma cells via an Akt-dependent mechanism.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 24;435(1):107-12. doi: 10.1016/j.bbrc.2013.04.049. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.04.049](http://1016/j.bbrc.2013.04.049)

**AUTORES / AUTHORS:** - Yang YL; Huang PH; Chiu HC; Kulp SK; Chen CS; Kuo CJ; Chen HD; Chen CS

**INSTITUCIÓN / INSTITUTION:** - Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

**RESUMEN / SUMMARY:** - Epigenetic regulation via abnormal activation of histone deacetylases (HDACs) is a mechanism that leads to cancer initiation and promotion. Activation of HDACs results in transcriptional upregulation of human telomerase reverse transcriptase (hTERT) and increases telomerase activity during cellular immortalization and tumorigenesis. However, the effects of HDAC inhibitors on the transcription of hTERT vary in different cancer cells. Here, we studied the effects of a novel HDAC inhibitor, AR42, on telomerase activity in a PTEN-null U87MG glioma cell line. AR42 increased hTERT mRNA in U87MG glioma cells, but suppressed total telomerase activity in a dose-dependent manner. Further analyses suggested that AR42 decreases the phosphorylation of hTERT via an Akt-dependent mechanism. Suppression of Akt phosphorylation and telomerase activity was also observed with PI3K inhibitor LY294002 further supporting the hypothesis that Akt signaling is involved in suppression of AR42-induced inhibition of telomerase activity. Finally, ectopic expression of a constitutive active form of Akt restored telomerase activity in AR42-treated cells. Taken together, our results

demonstrate that the novel HDAC inhibitor AR42 can suppress telomerase activity by inhibiting Akt-mediated hTERT phosphorylation, indicating that the PI3K/Akt pathway plays an important role in the regulation of telomerase activity in response to this HDAC inhibitor.

[370]

**TÍTULO / TITLE:** - Extracellular signal-regulated kinase 2 mediates the expression of granulocyte colony-stimulating factor in invasive cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):419-24. doi: 10.3892/or.2013.2463. Epub 2013 May 14.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2463](#)

**AUTORES / AUTHORS:** - Lee CH; Lin SH; Chang SF; Chang PY; Yang ZP; Lu SC

**INSTITUCIÓN / INSTITUTION:** - National Institute of Cancer Research, National Health Research Institutes, Zhunan, Miaoli County 35053, Taiwan, R.O.C.

**RESUMEN / SUMMARY:** - Granulocyte colony-stimulating factor (G-CSF) affects granulopoiesis and is important for mobilizing neutrophils into blood circulation. Due to the hematopoietic properties of G-CSF, it has been widely used to clinically treat chemotherapy-induced neutropenia. However, G-CSF can promote tumors by inhibiting innate and adaptive immunity and enhancing angiogenesis and neoplastic growth. Most G-CSF-producing tumors are associated with a poor prognosis. This indicates that G-CSF promotes cancer progression. Thus, identifying regulatory molecules involved in tumor-derived G-CSF expression may provide therapeutic targets for cancer treatment. This study identified considerable G-CSF expression in malignant breast, lung and oral cancer cells. However, G-CSF expression was barely detectable in non-invasive cell lines. Expression of G-CSF mRNA and protein increased during exposure to tumor necrosis factor-alpha (TNF-alpha). Treatment with U0126 (a mitogen-activated protein kinase inhibitor) drastically reduced basal levels of G-CSF and TNF-alpha-induced G-CSF in aggressive cancer cells. This study also showed that knockdown of extracellular signal-regulated kinase (ERK) 2 by shRNA was necessary and sufficient to eliminate the expression of tumor-derived G-CSF. This did not apply to ERK1. Therefore, ERK2 (but not ERK1) is responsible for the transcriptional regulation of tumor-derived G-CSF. The results indicate the pharmaceutical value of specific ERK2 inhibitors in treating patients with G-CSF-producing tumors.

[371]

**TÍTULO / TITLE:** - Sipa1 promoter polymorphism predicts risk and metastasis of lung cancer in Chinese.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 May 9. doi: 10.1002/mc.22039.

●●Enlace al texto completo (gratis o de pago) [1002/mc.22039](http://1002/mc.22039)

**AUTORES / AUTHORS:** - Xie C; Yang L; Yang X; Yang R; Li Y; Qiu F; Chen M; Fang W; Bin X; Deng J; Huang D; Liu B; Zhou Y; Lu J

**INSTITUCIÓN / INSTITUTION:** - The Institute for Chemical Carcinogenesis, The State Key Lab of Respiratory Disease, Guangzhou Medical University, Guangzhou, P.R., China; Dongguan Taiping People Hospital, Dongguan, P.R., China.

**RESUMEN / SUMMARY:** - Signal-induced proliferation associated gene 1 (Sipa1) is a signal transducer to activate the Ras-related proteins and modulate cell progression, differentiation, adhesion and cancer metastasis. In this study, we tested the hypothesis that single nucleotide polymorphisms (SNPs) in Sipa1 are associated with lung cancer risk and metastasis. Three common SNPs (rs931127A > G, rs2448490G > A, and rs3741379G > T) were genotyped in a discovery set of southern Chinese population and then validated the promising SNPs in a validation set of an eastern Chinese population in a total of 1559 lung cancer patients and 1679 cancer-free controls. The results from the two sets were consistent, the rs931127GG variant genotype had an increased risk of lung cancer compared to the rs931127AA/GA genotypes (OR = 1.27; 95% CI = 1.09-1.49) after combination of the two populations, and the rs931127GG interacted with pack-year smoked on increasing lung cancer risk (P = 0.037); this SNP also had an effect on patients' clinical stages (P = 0.012) that those patients with the rs931127GG genotype had a significant higher metastasis rate and been advanced N, M stages at diagnosis. However, these associations were not observed for rs2448490G > A and rs3741379G > T in the discovery set. Our data suggest that the SNP rs931127A > G in the promoter of Sipa1 was significantly associated with lung cancer risk and metastasis, which may be a biomarker to predict the risk and metastasis of lung cancer. © 2013 Wiley Periodicals, Inc.

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[372]

**TÍTULO / TITLE:** - Use of pharmacogenetics for predicting cancer prognosis and treatment exposure, response and toxicity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hum Genet. 2013 May 16. doi: 10.1038/jhg.2013.42.

●●Enlace al texto completo (gratis o de pago) [1038/jhg.2013.42](http://1038/jhg.2013.42)

**AUTORES / AUTHORS:** - Hertz DL; McLeod HL

**INSTITUCIÓN / INSTITUTION:** - 1] UNC Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [2] Department of Clinical, Social and Administrative Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA.

**RESUMEN / SUMMARY:** - Cancer treatment is complicated because of a multitude of treatment options and little patient-specific information to help clinicians choose appropriate therapy. There are two genomes relevant in cancer

treatment: the tumor (somatic) and the patient (germline). Together, these two genomes dictate treatment outcome through four processes: the somatic genome primarily determines tumor prognosis and response while the germline genome modulates treatment exposure and toxicity. In this review, we describe the influence of these genomes on treatment outcomes by highlighting examples of genetic variation that are predictors of each of these four factors, prognosis, response, toxicity and exposure, and discuss the translation and clinical implementation of each. Use of pre-treatment pharmacogenetic testing will someday enable clinicians to make individualized therapy decisions about aggressiveness, drug selection and dose, improving treatment outcomes for cancer patients. *Journal of Human Genetics* advance online publication, 16 May 2013; doi:10.1038/jhg.2013.42.

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[373]

**TÍTULO / TITLE:** - The role of a ginseng saponin metabolite as a DNA methyltransferase inhibitor in colorectal cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Int J Oncol.* 2013 Jul;43(1):228-36. doi: 10.3892/ijo.2013.1931. Epub 2013 May 2.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1931](#)

**AUTORES / AUTHORS:** - Kang KA; Kim HS; Kim DH; Hyun JW

**INSTITUCIÓN / INSTITUTION:** - School of Medicine and Institute for Nuclear Science and Technology, Jeju National University, Jeju 690-756, Republic of Korea.

**RESUMEN / SUMMARY:** - Hypermethylation of runt-related transcription factor 3 (RUNX3) promoter regions occurs in at least 65% of colorectal cancer cell lines. Compound K, the main metabolite of ginseng saponin, induced demethylation of a RUNX3 promoter in HT-29 human colorectal cancer cells, assessed by methylation-specific PCR and the quantitative pyrosequencing analysis. The demethylation of RUNX3 in compound K-treated cells resulted in the re-expression of RUNX3 mRNA, protein and the localization into the nucleus. Demethylation of the RUNX3 gene by compound K occurred via inhibition of the expression and activity of DNA methyltransferase 1 (DNMT1). Compound K also significantly induced RUNX3-mediated expression of Smad4 and Bim. DNMT1 inhibitory activity by compound K was related to extracellular signal-regulated kinase (ERK) inhibition, assessed by siRNA transfection on DNMT1 and ERK. In conclusion, compound K significantly inhibits the growth of colorectal cancer cells by inhibiting DNMT1 and reactivating epigenetically-silenced genes. Ginseng saponin is a potential candidate as DNMT1 inhibitor in the chemoprevention of cancer.

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[374]

**TÍTULO / TITLE:** - Erratum to: Induction of apoptosis with mitochondrial membrane depolarization by a glycyrrhetic acid derivative in human leukemia K562 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cytotechnology. 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1007/s10616-013-9554-](#)

[6](#)

**AUTORES / AUTHORS:** - Gao Z; Kang X; Hu J; Ju Y; Xu C

**INSTITUCIÓN / INSTITUTION:** - The Laboratory of Proteomics and Molecular Enzymology, College of Life Science, Zhejiang Sci-Tech University, Xiasha Higher Education Zone, Hangzhou, 310018, Zhejiang Province, China.

[375]

**TÍTULO / TITLE:** - Dysregulation of BMI1 and microRNA-16 collaborate to enhance an anti-apoptotic potential in the side population of refractory mantle cell lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncogene. 2013 May 20. doi: 10.1038/onc.2013.177.

●●Enlace al texto completo (gratis o de pago) [1038/onc.2013.177](#)

**AUTORES / AUTHORS:** - Teshima K; Nara M; Watanabe A; Ito M; Ikeda S; Hatano Y; Oshima K; Seto M; Sawada K; Tagawa H

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Nephrology and Rheumatology, Akita University Graduate School of Medicine, Akita, Japan.

**RESUMEN / SUMMARY:** - The proto-oncogene BMI1 and its product, Bmi1, is overexpressed in various types of tumors, particularly in aggressive tumors and tumors resistant to conventional chemotherapy. BMI1/Bmi1 is also crucially involved in cancer-initiating cell maintenance, and is recurrently upregulated in mantle cell lymphoma (MCL), especially aggressive variants. Recently, side population (SP) cells were shown to exhibit tumor-initiating characteristics in various types of tumors. In this study, we show that recurrent MCL cases significantly exhibit upregulation of BMI1/Bmi1. We further demonstrate that clonogenic MCL SP shows such tumor-initiating characteristics as high tumorigenicity and self-renewal capability, and that BMI1 was upregulated in the SP from recurrent MCL cases and MCL cell lines. On screening for upstream regulators of BMI1, we found that expression of microRNA-16 (miR-16) was downregulated in MCL SP cells by regulating Bmi1 in the SPs, leading to reductions in tumor size following lymphoma xenografts. Moreover, to investigate downstream targets of BMI1 in MCL, we performed cross-linking/chromatin immunoprecipitation assay against MCL cell lines and demonstrated that Bmi1 directly regulated pro-apoptotic genes such as BCL2L11/Bim and PMAIP1/Noxa, leading to enhance anti-apoptotic potential of MCL. Finally, we found that a proteasome inhibitor bortezomib, which has been recently used for relapsed MCL, effectively induced apoptosis among MCL cells

while reducing expression of Bmi1 and increasing miR-16 in MCL SP. These results suggest that upregulation of BMI1 and downregulation of miR-16 in MCL SP has a key role in the disease's progression by reducing MCL cell apoptosis. Our results provide important new insight into the pathogenesis of MCL and strongly suggest that targeting BMI1/Bmi1 might be an effective approach to treating MCL, particularly refractory and recurrent cases. Oncogene advance online publication, 20 May 2013; doi:10.1038/onc.2013.177.

[376]

**TÍTULO / TITLE:** - Up-regulation of urinary markers predict outcome in IgA nephropathy but their predictive value is influenced by treatment with steroids and azathioprine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Nephrol. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [5414/CN107836](#)

**AUTORES / AUTHORS:** - Stangou M; Papagianni A; Bantis C; Moisiadis D; Kasimatis S; Spartalis M; Pantzaki A; Efstratiadis G; Memmos D

**RESUMEN / SUMMARY:** - Objective: Steroids and immunosuppressants can delay progression of renal function in IgAN, but their possible effect in local cytokines has not been studied. Material and methods: Histology in 53 IgAN patients (M/F 35/18 age 40.5 years (17 - 65)) was evaluated using the Oxford classification system. IL-1beta, -2, -4, -5, -6, -10, -12 and -17, INF-gamma and MCP-1 were measured subsequently by multiplex cytokine assay in first morning urine samples taken at the day of renal biopsy. After a 6-month course with RAASinhibitors + fish oils (FO), 35/53 patients, Group A, responded and continued on the same treatment, while in 18/53 who did not respond, Group B, steroids + azathiopine were added. Results: The presence of endocapillary proliferation had significant correlation with the urinary excretion of pro-inflammatory and pro-fibrotic cytokines (IL-1beta, MCP-1, IL-17, INF-gamma, IL-6 and IL-10). Serum creatinine at time of diagnosis had significant correlation with proteinuria (p = 0.02), urinary levels of IL-1beta (p = 0.03), IL-2 (p = 0.01) and MCP-1 (p = 0.03). GFR was reduced from 65 +/- 29 to 57 +/- 34 ml/min, p = 0.005 in Group A and remained stable in Group B patients (GFR from 63 +/- 24 to 61 +/- 30 ml/min, p = NS). Most of the measured cytokines in the urine predicted deterioration of renal function in Group A, but the urinary excretion of IL-6 seemed to predict renal function outcome in both groups of patients. Conclusion: Several cytokines are excreted in the urine of patients with IgAN, and their levels predict the outcome of the disease. Steroids + aza may exert their beneficial effect through suppression of the production or activation of most cytokines.

[377]

**TÍTULO / TITLE:** - 4-Chlorobenzoyl berbamine, a novel berbamine derivative, induces apoptosis in multiple myeloma cells through the IL-6 signal transduction pathway and increases FOXO3a-Bim expression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):425-32. doi: 10.3892/or.2013.2431. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2431](#)

**AUTORES / AUTHORS:** - Shen JK; Du HP; Ma Q; Yang M; Wang YG; Jin J

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Institute of Hematology, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, P.R. China.

**RESUMEN / SUMMARY:** - Multiple myeloma (MM) is an incurable hematopoietic malignancy, although many novel therapeutic agents have been explored. In the present study, we showed that 4-chlorobenzoyl berbamine (BBD9), a novel derivative of berbamine, inhibited the growth of 4 MM cell lines (U266, RPMI 8226, MM1.R and MM1.S). After a 24h treatment with BBD9, the half maximal inhibitory concentration (IC50) values were 1.8, 2.3, 1.5 and 2.4 microg/ml, respectively, using MTT assays. In BBD9-treated U266 and RPMI 8226 cells, Annexin V (AV)-propidium iodide (PI) staining and FACS analysis demonstrated that apoptosis was involved in this inhibition. This was confirmed by western blot analysis indicating activation and cleavage of caspase-3, -8, -9 and PARP. BBD9 also induced G2/M phase cell cycle arrest in these cells. To investigate the mechanisms responsible for BBD9-induced apoptosis, U266 cells were incubated with 0, 1 or 2 microg/ml of BBD9 combined with 0 or 150 ng/ml of interleukin (IL)-6. MTT assays showed that IL-6 partially abrogated the BBD9-induced cell growth inhibition. Furthermore, BBD9 inhibited autocrine IL-6 production, and downregulated membrane IL6 receptor (IL-6R) expression. Crucial proteins downstream of the IL-6 signaling pathway, including AKT and STAT3, were inactivated in BBD9-treated U266 cells, although exogenous IL-6 did not abrogate this effect. Forkhead transcription factor class 3a (FOXO3a), a nuclear transcription factor downstream from AKT, was upregulated in the nuclei of BBD9-treated U266 cells. Bim, the target gene of FOXO3a, was upregulated at both the protein and mRNA levels, as shown by western blot analysis and quantitative PCR. These results suggest that BBD9 induces apoptosis in MM cells through the inhibition of the IL-6 signaling pathway, leading to FOXO3a activation and upregulation of pro-apoptotic Bim.

[378]

**TÍTULO / TITLE:** - RU486, a glucocorticoid receptor antagonist, induces apoptosis in U937 human lymphoma cells through reduction in mitochondrial membrane potential and activation of p38 MAPK.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):506-12. doi: 10.3892/or.2013.2432. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2432](https://doi.org/10.3892/or.2013.2432)

**AUTORES / AUTHORS:** - Jang JH; Woo SM; Um HJ; Park EJ; Min KJ; Lee TJ; Kim SH; Choi YH; Kwon TK

**INSTITUCIÓN / INSTITUTION:** - Department of Immunology, School of Medicine, Keimyung University, Dalseo-Gu, Daegu, Republic of Korea.

**RESUMEN / SUMMARY:** - RU486 (mifepristone) exerts an anticancer effect on cancer cells via induction of apoptosis. However, the molecular mechanisms are not fully understood. Here, we investigated the effect of RU486 on the apoptosis of U937 human leukemia cells. RU486 markedly increased apoptosis in U937 cells as well as in MDA231 human breast carcinoma, A549 human lung adenocarcinoma epithelial and HCT116 human colorectal carcinoma cells. RU486 increased dose-dependent release of mitochondrial cytochrome c, and reduced the mitochondrial membrane potential (MMP, Deltapsim) in RU486-treated U937 cells. We also found that overexpression of Bcl-2 completely blocked RU486-mediated apoptosis. However, reactive oxygen species signaling had no effect on RU486-induced apoptosis. RU486 increased the phosphorylation of p38 MAPK and JNK, but p38 MAPK only was associated with RU486-mediated apoptosis. Taken together, RU486 induces apoptosis through reduction in the mitochondrial membrane potential and activation of p38 MAPK in U937 human leukemia cells.

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[379]

**TÍTULO / TITLE:** - In vivo molecular imaging with cetuximab, an anti-EGFR antibody, for prediction of response in xenograft models of human colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Endoscopy. 2013 Jun;45(6):469-77. doi: 10.1055/s-0032-1326361. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1055/s-0032-1326361](https://doi.org/10.1055/s-0032-1326361)

**AUTORES / AUTHORS:** - Goetz M; Hoetker MS; Diken M; Galle PR; Kiesslich R

**INSTITUCIÓN / INSTITUTION:** - I. Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz, Mainz, Germany.

**RESUMEN / SUMMARY:** - Background and study aims: Molecular imaging has mainly been studied for detection of lesions using diagnostic probes. The aim of the current trial was to evaluate in vivo confocal laser endomicroscopy (CLE) with cetuximab, an antibody targeting the epidermal growth factor receptor (EGFR), for detection and moreover early prediction of response to molecular chemotherapy in models of human colorectal cancer (CRC). Methods: Xenografts with cetuximab-sensitive (HT29) and cetuximab-resistant (SW620) human CRC cell lines were induced in 44 mice. CLE was performed 48 h after injection of a fluorescently labelled cetuximab test dose, and compared with

isotype antibody or untreated controls on d0, and d30 (HT29) or d15 (SW620). Initial fluorescence intensity was examined in relation to clinical readouts (tumor growth, thriving, mortality) during cetuximab treatment vs. controls. Results were validated in vivo with wide-field molecular imaging in three HT29 mice and ex vivo using fluorescence-activated cell sorting (FACS) and immunohistochemistry. Results: All HT29 xenografts showed specific fluorescence in vivo after cetuximab injection on d0 and d30. Fluorescence at d0 was significantly stronger in cetuximab-treated HT29 tumors than in HT29 controls ( $P = 0.0017$ ) or cetuximab-treated SW620 tumors ( $P = 0.0027$ ), and accorded with significantly slower tumor progression ( $P = 0.0009$ ), better overall survival ( $P = 0.02$ ), and better physical condition ( $P < 0.0001$ ). Cetuximab sensitivity could be predicted from fluorescence intensity at d0 with high positive predictive value. Conclusions: Molecular CLE was for the first time linked to early prediction of response to targeted therapy in models of human CRC. Therapeutic antibodies can be used as molecular beacons in CLE and wide-field techniques. These results may indicate a promising principle for early patient stratification.

[380]

**TÍTULO / TITLE:** - Homoharringtonine in combination with cytarabine and aclarubicin in the treatment of refractory/relapsed acute myeloid leukemia: a single-center experience.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1758-](#)

[5](#)

**AUTORES / AUTHORS:** - Yu W; Mao L; Qian J; Qian W; Meng H; Mai W; Tong H; Tong Y; Jin J

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, the First Affiliated Hospital, Zhejiang University College of Medicine, No. 79 Qingchun Road, 310003, Hangzhou, Zhejiang, People's Republic of China.

**RESUMEN / SUMMARY:** - To assess the efficacy and toxicity of HAA regimen (Homoharringtonine 4 mg/m<sup>2</sup>/day, days 1-3; cytarabine 150 mg/m<sup>2</sup>/day, days 1-7; aclarubicin 12 mg/m<sup>2</sup>/day, days 1-7) as a salvage therapy in the treatment of refractory and/or relapsed acute myeloid leukemia (AML), 46 patients with refractory and/or relapsed AML, median age 37 (16-65) years, participated in this clinical study. The median follow-up was 41 (10-86) months. Eighty percent of patients achieved complete remission (CR), and the first single course of re-induction HAA regimen resulted in CR rate of 76.1 %. The study protocol allowed two courses of induction. The CR rates of patients with favorable, intermediate and unfavorable cytogenetics were 90 %, 88.9 %, and 37.5 %, respectively. For all patients, the estimated 3-year overall survival (OS) rate was 42 %, and the estimated relapse free survival (RFS) at 3 years for the 36 CR

cases was 49 %. The toxicities associated with HAA regimen were acceptable. HAA is a good choice in cases with refractory/relapsing AML for salvage chemotherapy, preferably with a high-efficacy and low-toxicity profile.

[381]

**TÍTULO / TITLE:** - Knockdown of interferon-induced transmembrane protein 3 expression suppresses breast cancer cell growth and colony formation and affects the cell cycle.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):171-8. doi: 10.3892/or.2013.2428. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2428](#)

**AUTORES / AUTHORS:** - Yang M; Gao H; Chen P; Jia J; Wu S

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, The Second Hospital of Jilin University, Changchun, Jilin 130041, P.R. China.

**RESUMEN / SUMMARY:** - Interferon-induced transmembrane protein 3 (IFITM3) is an important anti-virus protein and has been recently shown to play a role in human cancer development. Thus, the present study aimed to assess the expression of the IFITM3 protein in breast cancer tissues and to investigate the in vitro effects of IFITM3 knockdown in the regulation of breast cancer cell growth and cell cycle distributions. A total of 64 patients of breast cancer and the matched normal tissue specimens were obtained for immunohistochemical analysis of IFITM3 expression. Lentivirus-carrying IFITM3 shRNA was used to knock down IFITM3 expression in breast cancer cell lines. Phenotypic changes of cell viability, growth, colony formation and cell cycle distribution was also assayed using flow cytometry, MTT, BrdU incorporation and colony formation assays. The IFITM3 protein was highly expressed in invasive breast cancer compared to normal tissues and was significantly associated with estrogen receptor and progesterone receptor status. The lentivirus-carried IFITM3 shRNA significantly reduced the expression of IFITM3 mRNA and protein in breast cancer cells, inhibiting tumor cell viability, growth and colony formation, arrested tumor cells at the G0/G1 phase of the cell cycle and reduced the number of cells in the S phase of the cell cycle. Expression of IFITM3 protein could be a potential therapeutic target in future treatment of breast cancer.

[382]

**TÍTULO / TITLE:** - Lactate Dehydrogenase B: A Metabolic Marker of Response to Neoadjuvant Chemotherapy in Breast Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0623](#)

**AUTORES / AUTHORS:** - Dennison JB; Molina JR; Mitra S; Gonzalez-Angulo AM; Balko JM; Kuba MG; Sanders ME; Pinto JA; Gomez HL; Arteaga CL; Brown RE; Mills GB

**INSTITUCIÓN / INSTITUTION:** - Experiment Therapeutics, MD Anderson.

**RESUMEN / SUMMARY:** - **PURPOSE:** Although breast cancers are known to be molecularly heterogeneous, their metabolic phenotype is less well understood and may predict response to chemotherapy. This study aimed to evaluate metabolic genes as individual predictive biomarkers in breast cancer. **Methods:** mRNA microarray data from breast cancer cell lines were used to identify bimodal genes - those with highest potential for robust high/low classification in clinical assays. Metabolic function was evaluated in vitro for the highest scoring metabolic gene, lactate dehydrogenase B (LDHB). Its expression was associated with neoadjuvant chemotherapy response and relapse within clinical and PAM50-derived subtypes. **RESULTS:** LDHB was highly expressed in cell lines with glycolytic, basal-like phenotypes. Stable knockdown of LDHB in cell lines reduced glycolytic dependence, linking LDHB expression directly to metabolic function. Using patient datasets, LDHB was highly expressed in basal-like cancers and could predict basal-like subtype within clinical groups (odds ratio = 21 for hormone-receptor (HR)-positive/HER2-negative; odds ratio = 10 for triple-negative). Furthermore, high LDHB predicted pathological complete response (pCR) to neoadjuvant chemotherapy for both HR-positive/HER2-negative (odds ratio = 4.1,  $P < .001$ ) and triple-negative (odds ratio = 3.0,  $P = .003$ ) cancers. For triple-negative tumors without pCR, high LDHB post-treatment also identified proliferative tumors with increased risk of recurrence (hazard ratio = 2.2,  $P = .006$ ). **CONCLUSIONS:** Expression of LDHB predicted response to neoadjuvant chemotherapy within clinical subtypes independently of standard prognostic markers and PAM50-subtyping. These observations support prospective clinical evaluation of LDHB as a predictive marker of response for breast cancer patients receiving neoadjuvant chemotherapy.

[383]

**TÍTULO / TITLE:** - Tetrandrine induces cell death in SAS human oral cancer cells through caspase activation-dependent apoptosis and LC3-I and LC3-II activation-dependent autophagy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 May 21. doi: 10.3892/ijo.2013.1952.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1952](#)

**AUTORES / AUTHORS:** - Huang AC; Lien JC; Lin MW; Yang JS; Wu PP; Chang SJ; Lai TY

**INSTITUCIÓN / INSTITUTION:** - Department of Nursing, St. Mary's Junior College of Medicine, Nursing and Management, Yilan, Taiwan, R.O.C.

**RESUMEN / SUMMARY:** - Numerous studies have demonstrated that autophagy is associated with cancer development. Thus, agents to induce autophagy could be employed in some cases for the treatment of cancer. Our results showed that tetrandrine significantly decreased the viability of SAS cells in a concentration- and time-dependent manner. Tetrandrine induced nuclear condensation, demonstrated by DAPI staining. The early events in apoptosis analysed by Annexin V/PI staining indicated that the percentage of cells staining positive for Annexin V was slightly increased in SAS cells with tetrandrine treatment but was much lower following bafilomycin A1 pre-treatment. Tetrandrine caused AVO and MDC induction in SAS cells in a concentration-dependent manner by fluorescence microscopy. Tetrandrine also caused LC-3 expression in SAS cells in a time-dependent manner. Our results show that tetrandrine treatment induced the levels of cleaved caspase-3 in a concentration- and time-dependent manner. Tetrandrine treatment induced the levels of LC-3 II, Atg-5, beclin-1, p-S6, p-ULK, p-mTOR, p-Akt (S473) and raptor. Tetrandrine decreased cell viability, but bafilomycin A1, 3-MA, chloroquine and NAC protected tetrandrine-treated SAS cells against decrease of cell viability. Atg-5, beclin-1 siRNA decreased tetrandrine-induced cleaved caspase-3 and cleaved PARP in SAS cells and protected tetrandrine-treated SAS cells against decrease in cell viability. Chloroquine, NAC and bafilomycin A1 also decreased tetrandrine-induced cleaved caspase-3 and cleaved PARP in SAS cells. Our results indicate the tetrandrine induces apoptosis and autophagy of SAS human cancer cells via caspase-dependent and LC3-I and LC3-IIdependent pathways.

[384]

**TÍTULO / TITLE:** - Chidamide, a novel histone deacetylase inhibitor, synergistically enhances gemcitabine cytotoxicity in pancreatic cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Apr 26;434(1):95-101. doi: 10.1016/j.bbrc.2013.03.059. Epub 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.03.059](http://1016/j.bbrc.2013.03.059)

**AUTORES / AUTHORS:** - Qiao Z; Ren S; Li W; Wang X; He M; Guo Y; Sun L; He Y; Ge Y; Yu Q

**INSTITUCIÓN / INSTITUTION:** - Beijing Institute of Transfusion Medicine, Beijing, PR China; College of Life Science, Jilin University, Changchun, PR China.

**RESUMEN / SUMMARY:** - Pancreatic cancer is a lethal human malignancy with an extremely poor prognosis and urgently requires new therapies. Histone deacetylase inhibitors (HDACIs) represent a new class of anticancer agents and have shown promising antitumor activities in preclinical models of pancreatic cancer. In this study, we sought to determine the antitumor effects of a novel HDACI, chidamide (CS055), in pancreatic cancer cells alone or in combination with gemcitabine. Treatments of BxPC-3 or PANC-1 pancreatic cancer cell lines

with chidamide resulted in dose- and time-dependent growth arrest, accompanied by induction of p21 expression. When combined in a sequential schedule, chidamide synergistically enhanced gemcitabine-induced cell growth arrest and apoptosis, accompanied by cooperative downregulation of Mcl-1 and loss of mitochondrial membrane potential (DeltaPsi<sub>m</sub>). Chidamide enhanced gemcitabine-induced DNA double-strand breaks and S phase arrest, and abrogated the G2/M cell cycle checkpoint, potentially through suppression of CHK1 expression. Our results suggest that chidamide has a therapeutic potential for treating pancreatic cancer, especially in combination with gemcitabine.

[385]

**TÍTULO / TITLE:** - Postoperative Nodal Status and Diffuse-type Histology Are Independent Prognostic Factors in Resectable Advanced Gastric Carcinomas After Preoperative Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Surg Pathol. 2013 May 24.

●●Enlace al texto completo (gratis o de pago)

[1097/PAS.0b013e31828778fd](#)

**AUTORES / AUTHORS:** - Koh YW; Park YS; Ryu MH; Ryoo BY; Park HJ; Yook JH; Kim BS; Kang YK

**INSTITUCIÓN / INSTITUTION:** - Departments of \*Pathology daggerOncology double daggerSurgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - Surgical resection of primary gastric lesions after neoadjuvant or palliative chemotherapy is performed for curative or palliative purpose in locally advanced (LA) or initially metastatic (IM) gastric cancer. We investigated which histomorphologic features were associated with patient prognosis. We examined 143 patients (57 LA and 86 IM) who underwent gastrectomy after chemotherapy between 2000 and 2009. The tumor regression grade (TRG)-determined by examining the residual neoplastic cells and background stromal changes-was evaluated. Progression-free (PFS) and overall survival (OS) were evaluated according to pretherapeutic and posttherapeutic clinicopathologic factors using univariate and multivariate analyses. Because both the LA and the IM groups showed similar trends of PFS and OS according to TRG, the 2 groups were analyzed together. Patients with TRG1 (no residual primary tumor) showed a superior PFS and OS than the remaining TRGs. We defined pathologic complete regression (pCR) as TRG1 with negative lymph nodes (LN) and the others as non-pCR. Sixteen patients (11.1%) had pCR with better PFS (P=0.007) and OS (P=0.006). Initial disease status (LA or IM) remained as independent prognostic factors for PFS (P=0.021) but not for OS (P=0.109). The postoperative negative LN status correlated with good outcome and postoperative diffuse-type histology

correlated with poor outcome after multivariate analysis. This study showed that pCR, but not partial regression, provides meaningful prognostic information in gastrectomy after chemotherapy. In addition, postoperative LN positivity and diffuse-type histology were independent poor prognostic factors for PFS and OS.

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[386]

**TÍTULO / TITLE:** - Melatonin overcomes apoptosis resistance in human hepatocellular carcinoma by targeting Survivin and XIAP.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pineal Res. 2013 Apr 24. doi: 10.1111/jpi.12060.

●●Enlace al texto completo (gratis o de pago) [1111/jpi.12060](http://1111/jpi.12060)

**AUTORES / AUTHORS:** - Fan L; Sun G; Ma T; Zhong F; Wei W

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China.

**RESUMEN / SUMMARY:** - Apoptosis resistance in hepatocellular carcinoma (HCC) is one of the most significant factors for hepatocarcinogenesis and tumor progression, and leads to resistance to conventional chemotherapy. It is well known that inhibitor of apoptosis proteins (IAPs) play key roles in apoptosis resistance, it has become an important target for antitumor therapy. In this study, we examined if melatonin, the main secretory product of the pineal gland, targeted IAPs, leading to the inhibition of apoptosis resistance. To accomplish this, we first observed that four members of IAPs (cIAP-1, cIAP-2, Survivin, and XIAP) were overexpressed in human HCC tissue. Interestingly, melatonin significantly inhibited the growth of HepG2 and SMMC-7721 cells and promoted apoptosis along with the downregulation of Survivin and XIAP, but had no effect on the expression of cIAP-1 and cIAP-2. These data suggest that the inhibition of Survivin and XIAP by melatonin may play an important part in reversing apoptosis resistance. Notably, cIAP-1, Survivin and XIAP were significantly associated with the coexpression of COX-2 in human HCC specimens. Melatonin also reduced the expression of COX-2 and inhibited AKT activation in HepG2 and SMMC-7721 cells. Inhibition of COX-2 activity with the selective inhibitor, NS398, and inhibition of AKT activation using the PI3K inhibitor, LY294002, in tumor cells confirmed that melatonin-induced apoptosis was COX-2/PI3K/AKT-dependent, suggesting that the COX-2/PI3K/AKT pathway plays a role in melatonin inhibition of IAPs. Taken together, these results suggest that melatonin overcomes apoptosis resistance by the suppressing Survivin and XIAP via the COX-2/PI3K/AKT pathway in HCC cells.

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[387]

**TÍTULO / TITLE:** - CXC chemokine receptor 4 is essential for maintenance of renal cell carcinoma-initiating cells and predicts metastasis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Stem Cells. 2013 Apr 30. doi: 10.1002/stem.1407.

●●Enlace al texto completo (gratis o de pago) [1002/stem.1407](http://1002/stem.1407)

**AUTORES / AUTHORS:** - Gassenmaier M; Chen D; Buchner A; Henkel L; Schiemann M; Mack B; Schendel DJ; Zimmermann W; Pohla H

**INSTITUCIÓN / INSTITUTION:** - Tumor Immunology Laboratory, LIFE Center, Ludwig-Maximilians-Universität, Munich, Germany.

**RESUMEN / SUMMARY:** - In many solid tumors, cancer stem cells (CSC) represent a small cell population with tumor-initiating, self-renewal and differentiation potential, which can be identified by surface protein markers. No generally applicable markers are yet known for renal cell carcinoma (RCC). Two RCC cell lines (RCC-26, RCC-53) were found to differ widely in their capacity to form spheres in vitro and to establish tumors in mice, potentially reflecting differences in CSC content. A subpopulation expressing the CXC chemokine receptor 4 (CXCR4) was present only in the more tumorigenic cell line RCC-53. When grown as spheres, most of the RCC-53 cells were CXCR4-positive, expressed stem cell-associated transcription factor genes at elevated levels and were more resistant towards the tyrosine kinase inhibitors sunitinib, sorafenib and pazopanib. Sorted CXCR4-positive cells exhibited greater capacity for sphere formation and tumor growth-inducing potential in vivo than CXCR4-negative cells. Significantly, higher CXCR4 mRNA levels in primary RCC tumors from patients with localized but not disseminated disease predicted longer survival. Downregulation of CXCR4 expression by siRNA or pharmacological inhibition by AMD3100 compromised tumor sphere formation, viability of CXCR4-positive cells and increased their responsiveness towards tyrosine kinase inhibitors. In conclusion, CXCR4 identifies a subpopulation of tumor-initiating cells in RCC cell lines and plays a role in their maintenance. The relative insensitivity of such cells to tyrosine kinase inhibitors might contribute to the development of therapy resistance in RCC patients. Future therapies therefore could combine blockade of the CXCR4 signaling pathway with standard therapies for more effective treatments of metastatic RCC.

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[388]

**TÍTULO / TITLE:** - Clinical study of the relationship between gamma-synuclein and the response of neoadjuvant chemotherapy in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Int Med Res. 2013 May 21.

●●Enlace al texto completo (gratis o de pago)

[1177/0300060513484434](http://1177/0300060513484434)

**AUTORES / AUTHORS:** - Wan F; Dong L; Zhang F; Wang Y; Chen F; Ni S; Chen Y; Long J

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

**RESUMEN / SUMMARY:** - OBJECTIVES: To investigate relationships between several protein biomarkers and clinical responses to neoadjuvant chemotherapy (NAC) in breast cancer. METHODS: Tumour tissue samples from female patients with locally advanced breast carcinoma (stages IIA to IIIC), treated with NAC regimens (including 5-fluorouracil, epirubicin, cyclophosphamide and docetaxel, epirubicin, cyclophosphamide) were analysed retrospectively. Immunohistochemical analysis was used to test for protein levels of oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER)-2, protein 53 (p53) and gamma-synuclein. Relationships between protein biomarkers and responses to NAC were analysed by multivariate logistic regression analysis. RESULTS: Data from 154 patients (median age, 51 years; range 27-75 years) were included. Multivariate logistic regression analysis showed that gamma-synuclein was an independent predictor of NAC objective response rate, and a statistically significant relationship was observed between NAC regimen, gamma-synuclein levels and pathological complete response rate. CONCLUSIONS: These study findings suggest that gamma-synuclein - in combination with other markers such as ER, PR and HER-2 - may serve as a biomarker for response to NAC in breast cancer and warrants further study.

[389]

**TÍTULO / TITLE:** - Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lancet Oncol. 2013 May 21. pii: S1470-2045(13)70162-1. doi: 10.1016/S1470-2045(13)70162-1.

●●Enlace al texto completo (gratis o de pago) [1016/S1470-2045\(13\)70162-1](#)

**AUTORES / AUTHORS:** - Ko YJ; Canil CM; Mukherjee SD; Winqvist E; Elser C; Eisen A; Reaume MN; Zhang L; Sridhar SS

**INSTITUCIÓN / INSTITUTION:** - Sunnybrook Odette Cancer Centre, Toronto, ON, Canada.

**RESUMEN / SUMMARY:** - BACKGROUND: No standard treatment exists for patients with platinum-refractory urothelial cancer. Taxanes and vinflunine are commonly used, but response is less than 20% with no survival benefit. In this phase 2 study, we assessed efficacy and tolerability of nanoparticle albumin-bound (nab) paclitaxel in platinum-refractory urothelial cancer. METHODS: We did an open-label, single-group, two-stage study at five centres in Canada. We enrolled patients aged at least 18 years with histologically confirmed, locally advanced, or metastatic measurable urothelial cancer, with documented progression on or within 12 months of treatment with one previous platinum-containing regimen. Patients received nab-paclitaxel at 260 mg/m<sup>2</sup>

intravenously every 3 weeks. Treatment continued until disease progression or occurrence of unacceptable toxic effects. The primary endpoint was objective tumour response, defined by a complete response (CR) or partial response (PR) according to Response Evaluation Criteria In Solid Tumors (version 1.0) criteria. Tumour response and safety were assessed in all patients who received at least one cycle of nab-paclitaxel. This study is registered with ClinicalTrials.gov, number NCT00683059. FINDINGS: We enrolled 48 patients between Oct 16, 2008, and June 23, 2010. Patients received a median of six cycles (range one to 15). 47 patients were evaluable; one (2.1%) had a CR and 12 (25.5%) had PRs, resulting in an overall response of 27.7% (95% CI 17.3-44.4). The most frequently recorded adverse events of any grade were fatigue (38 of 48; 79%), pain (37 of 48; 77%), alopecia (34 of 48; 71%), and neuropathy (30 of 48; 77%). The most frequently recorded adverse events of grade 3 or higher were pain (11 of 48; 23%), fatigue (five of 48; 23%), hypertension (three of 48; 6%), neuropathy (three of 48, 6%), and joint stiffness or pain (two of 48; 4%). INTERPRETATION: Nab-paclitaxel was well tolerated in this population of patients with pretreated advanced urothelial cancer with an encouraging tumour response. These results warrant further study of nab-paclitaxel in second-line treatment of urothelial cancer. FUNDING: Abraxis Bioscience, Celgene.

[390]

**TÍTULO / TITLE:** - Molecular characterization of anastrozole resistance in breast cancer: Pivotal role of the Akt/mTOR pathway in the emergence of de novo or acquired resistance and importance of combining the allosteric Akt inhibitor MK-2206 with an aromatase inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Mar 30. doi: 10.1002/ijc.28182.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28182](#)

**AUTORES / AUTHORS:** - Vilquin P; Villedieu M; Grisard E; Larbi SB; Ghayad SE; Heudel PE; Bachelot T; Corbo L; Treilleux I; Vendrell JA; Cohen PA

**INSTITUCIÓN / INSTITUTION:** - ISPB, Faculte de Pharmacie, Universite Lyon 1, Lyon, France; INSERM U1052, CNRS UMR5286, Centre de Recherche en Cancerologie de Lyon, Lyon, France.

**RESUMEN / SUMMARY:** - Acquisition of resistance to aromatase inhibitors (AIs) remains a major drawback in the treatment of estrogen receptor alpha (ERalpha)-positive breast cancers. The Res-Ana cells, a new model of acquired resistance to anastrozole, were established by long-term exposure of aromatase-overexpressing MCF-7 cells to this drug. These resistant cells developed ER-independent mechanisms of resistance and decreased sensitivity to the AI letrozole or to ERalpha antagonists. They also displayed a constitutive activation of the PI3K/Akt/mTOR pathway and a deregulated expression of several ErbB receptors. An observed increase in the phospho-

Akt/Akt ratio between primary and matched recurrent breast tumors of patients who relapsed under anastrozole adjuvant therapy also argued for a pivotal role of the Akt pathway in acquired resistance to anastrozole. Ectopic overexpression of constitutively active Akt1 in control cells was sufficient to induce de novo resistance to anastrozole. Strikingly, combining anastrozole with the highly selective and allosteric Akt inhibitor MK-2206 or with the mTOR inhibitor rapamycin increased sensitivity to this AI in the control cells and was sufficient to overcome resistance and restore sensitivity to endocrine therapy in the resistant cells. Our findings lead to us proposing a model of anastrozole-acquired resistance based on the selection of cancer-initiating-like cells possessing self-renewing properties, intrinsic resistance to anastrozole and sensitivity to MK-2206. Altogether, our work demonstrated that the Akt/mTOR pathway plays a key role in resistance to anastrozole and that combining anastrozole with Akt/mTOR pathway inhibitors represents a promising strategy in the clinical management of hormone-dependent breast cancer patients.

[391]

**TÍTULO / TITLE:** - PQ1, a quinoline derivative, induces apoptosis in T47D breast cancer cells through activation of caspase-8 and caspase-9.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Apoptosis. 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1007/s10495-013-0855-](#)

[1](#)

**AUTORES / AUTHORS:** - Ding Y; Nguyen TA

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Kansas State University, K244 Mosier Hall, 1800 Denison Avenue, Manhattan, KS, 66506, USA.

**RESUMEN / SUMMARY:** - Apoptosis, a programmed cell death, is an important control mechanism of cell homeostasis. Deficiency in apoptosis is one of the key features of cancer cells, allowing cells to escape from death. Activation of apoptotic signaling pathway has been a target of anti-cancer drugs in an induction of cytotoxicity. PQ1, 6-methoxy-8-[(3-aminopropyl)amino]-4-methyl-5-(3-trifluoromethylphenoxy)quinoline, has been reported to decrease the viability of cancer cells and attenuate xenograft tumor growth. However, the mechanism of the anti-cancer effect is still unclear. To evaluate whether the cytotoxicity of PQ1 is related to induction of apoptosis, the effect of PQ1 on apoptotic pathways was investigated in T47D breast cancer cells. PQ1-treated cells had an elevation of cleaved caspase-3 compared to controls. Studies of intrinsic apoptotic pathway showed that PQ1 can activate the intrinsic checkpoint protein caspase-9, enhance the level of pro-apoptotic protein Bax, and release cytochrome c from mitochondria to cytosol; however, PQ1 has no effect on the level of anti-apoptotic protein Bcl-2. Further studies also demonstrated that PQ1 can activate the key extrinsic player, caspase-8. Pre-

treatment of T47D cells with caspase-8 or caspase-9 inhibitor suppressed the cell death induced by PQ1, while pre-treatment with caspase-3 inhibitor completely counteracted the effect of PQ1 on cell viability. This report provides evidence that PQ1 induces cytotoxicity via activation of both caspase-8 and caspase-9 in T47D breast cancer cells.

[392]

**TÍTULO / TITLE:** - Rituximab activates Syk and AKT in CD20-positive B cell lymphoma cells dependent on cell membrane cholesterol levels.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Hematol. 2013 Apr 17. pii: S0301-472X(13)00159-8. doi: 10.1016/j.exphem.2013.04.006.

●●Enlace al texto completo (gratis o de pago)

[1016/j.exphem.2013.04.006](#)

**AUTORES / AUTHORS:** - Nozaki Y; Mitsumori T; Yamamoto T; Kawashima I; Shobu Y; Hamanaka S; Nakajima K; Komatsu N; Kirito K

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Oncology, University of Yamanashi, Yamanashi, Japan.

**RESUMEN / SUMMARY:** - The introduction of rituximab, an anti-CD20 monoclonal antibody, has dramatically improved the treatment outcomes of patients with B cell lymphoma. Nevertheless, the clinical response to rituximab varies, and a subpopulation of patients does not respond well to this antibody. Although several molecular events have been shown to be involved in the mechanism of action of rituximab, recent studies have demonstrated that intracellular signaling pathways and the direct effects of rituximab on cell membrane components are responsible for the antilymphoma action of this drug. In the present study, we demonstrated that rituximab activated Syk and Akt, molecules with antiapoptotic functions, in several CD20-positive lymphoma cell lines. Notably, rituximab activated Syk and Akt in all the tested primary lymphoma samples from six patients. Our results show that the cholesterol levels in lymphoma cell membranes have a crucial role in the regulation of Syk and Akt. The depletion of cholesterol from the cell membrane completely blocked rituximab-induced Syk and Akt activation. Simvastatin, an inhibitor of cholesterol synthesis, also abrogated rituximab-mediated Syk and Akt activation. Finally, we report that rituximab inhibited the apoptosis induced by chemotherapeutic drugs, which was observed solely in Akt-activated cells. This work demonstrates for the first time that rituximab paradoxically works to suppress apoptosis under certain conditions in a manner that is dependent on the cell membrane cholesterol level. Our observations provide novel insights and suggest that the cell membrane cholesterol level represents a new biomarker for predicting patient response to rituximab. Furthermore, the modulation of lipid rafts could provide a new strategy for enhancing the antilymphoma action of rituximab.

[393]

**TÍTULO / TITLE:** - Soluble biomarkers associated with response to treatment with tumor necrosis factor inhibitors in psoriatic arthritis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Rheumatol. 2013 Jun;40(6):866-71. doi: 10.3899/jrheum.121162. Epub 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [3899/jrheum.121162](#)

**AUTORES / AUTHORS:** - Chandran V; Shen H; Pollock RA; Pellett FJ; Carty A; Cook RJ; Gladman DD

**INSTITUCIÓN / INSTITUTION:** - From the Department of Medicine, Division of Rheumatology, University of Toronto; Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, Toronto; and the Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Ontario, Canada.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To identify soluble biomarkers associated with response to therapy with tumor necrosis factor inhibitors (TNFi) in patients with psoriatic arthritis (PsA). **METHODS:** The study was conducted at a PsA clinic where patients are assessed every 6 months, and serum samples are collected and stored once a year at the time of clinical assessment. Forty patients with active PsA who gave serum samples prior to treatment with TNFi and after at least 3 months of therapy were identified. Patients were classified as TNFi responders if tender joint count was < 3, swollen joint count was 0, and Psoriasis Area and Severity Index score was < 4 at the time the second sample was collected. The following biomarkers were tested by ELISA: TNF superfamily 14, matrix metalloproteinase-3 (MMP-3), receptor activator of nuclear factor kappa-B ligand, osteoprotegerin, cartilage oligomeric matrix protein (COMP), CII, C2C and C1-2C, CS-846, and highly sensitive C-reactive protein. Paired t tests and logistic regression was used for statistical analyses. **RESULTS:** After a mean treatment duration of 11 months with TNFi (etanercept 28 patients, adalimumab 6, golimumab 4, infliximab 2), 29 patients were classified as TNFi responders. Baseline level of MMP-3 was independently associated with responder status (OR 1.067 for each 1-unit increase, p = 0.045). A reduction in MMP-3 levels with therapy increased the odds of achieving response (OR 1.213 for each 1-unit change, p = 0.030), whereas a reduction in COMP decreased the odds (OR 0.587, for each 100-unit increase, p = 0.039). None of the other biomarkers was associated with response. **CONCLUSION:** Baseline as well as reduction in serum MMP-3 and increase in serum COMP are independently associated with response to TNFi therapy in patients with PsA.

[394]

**TÍTULO / TITLE:** - Estrogen receptor alpha is the major driving factor for growth in tamoxifen-resistant breast cancer and supported by HER/ERK signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 May;139(1):71-80. doi: 10.1007/s10549-013-2485-2. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2485-](#)

[2](#)

**AUTORES / AUTHORS:** - Thrane S; Lykkesfeldt AE; Larsen MS; Sorensen BS; Yde CW

**INSTITUCIÓN / INSTITUTION:** - Breast Cancer Group, Unit of Cell Death and Metabolism, Danish Cancer Society Research Center, Strandboulevarden 49, 2100, Copenhagen O, Denmark.

**RESUMEN / SUMMARY:** - Resistance to tamoxifen is a major clinical challenge in the treatment of breast cancer; however, it is still unclear which signaling pathways are the major drivers of tamoxifen-resistant growth. To characterize resistance mechanisms, we have generated different tamoxifen-resistant breast cancer cell lines from MCF-7. In this model, we investigated whether signaling from human epidermal growth factor receptors (HERs), their downstream kinases, or from the estrogen receptor alpha (ERalpha) was driving tamoxifen-resistant cell growth. Increased expression of EGFR and increased phosphorylation of HER3 were observed upon acquisition of tamoxifen resistance, and the extracellular activated kinase (ERK) signaling pathway was highly activated in the resistant cells. The EGFR inhibitor gefitinib and the ERK pathway inhibitor U0126 resulted in partial and preferential growth inhibition of tamoxifen-resistant cells. All the tamoxifen-resistant cell lines retained ERalpha expression but at a lower level compared to that in MCF-7. Importantly, we showed via ERalpha knockdown that the tamoxifen-resistant cells were dependent on functional ERalpha for growth and we observed a clear growth stimulation of resistant cell lines with clinically relevant concentrations of tamoxifen and 4-OH-tamoxifen, indicating that tamoxifen-resistant cells utilize agonistic ERalpha stimulation by tamoxifen for growth. The tamoxifen-resistant cells displayed high phosphorylation of ERalpha at Ser118 in the presence of tamoxifen; however, treatment with U0126 neither affected the level of Ser118 phosphorylation nor expression of the ERalpha target Bcl-2, suggesting that ERK contributes to cell growth independently of ERalpha in our cell model. In support of this, combined treatment against ERalpha and ERK signaling in resistant cells was superior to single-agent treatment and as effective as fulvestrant treatment of MCF-7 cells. Together, these findings demonstrate that ERalpha is a major driver of growth in tamoxifen-resistant cells supported by HER/ERK growth signaling, implying that combined targeting of these pathways may have a clinical potential for overcoming tamoxifen resistance.

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[395]

**TÍTULO / TITLE:** - Beta blockers and angiotensin-converting enzyme inhibitors' purported benefit on breast cancer survival may be explained by aspirin use.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):507-13. doi: 10.1007/s10549-013-2553-7. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2553-](#)

[7](#)

**AUTORES / AUTHORS:** - Holmes MD; Hankinson SE; Feskanich D; Chen WY

**INSTITUCIÓN / INSTITUTION:** - The Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA, 02115, USA, [michelle.holmes@channing.harvard.edu](mailto:michelle.holmes@channing.harvard.edu).

**RESUMEN / SUMMARY:** - Preclinical and epidemiologic evidence supports a possible role for beta-adrenergic blocking drugs (beta-blockers), and angiotensin-converting enzyme inhibitors (ACEIs) in promoting survival after breast cancer. However, these drugs are often used concurrently with aspirin, and there is a growing body of evidence indicating a survival benefit for aspirin. Therefore, we analyzed the use of beta-blockers and ACEIs after a breast cancer diagnosis and their association with breast cancer mortality, both individually, combined with each other, and in combination with aspirin use in the Nurses' Health Study, using updated measures of medication use and Cox proportional hazards models. There were 4,661 women with stages I-III breast cancer included; 292 breast cancer deaths occurred during median follow-up time of 10.5 years. Modeled individually, the multivariable relative risk and 95 % confidence intervals (RR, 95 % CI) for breast cancer death were (0.76, 0.54-1.05) for beta blockers, (0.89, 0.60-1.32) for ACEIs, and (0.46, 0.35-0.60) for aspirin. Modeled simultaneously, the multivariable (RR, 95 % CI) for breast cancer death were (0.83, 0.60-1.16) for beta blockers, (1.00, 0.68-1.46) for ACEIs, and (0.46, 0.35-0.61) for aspirin. We did not see a significant association with beta blockers and survival, but there was a suggestion. Our study was limited in that we could not assess type of beta blocker and the number of events among users was still quite low. We found no evidence of a protective effect for ACEIs. The strong protective association with aspirin use confounds the associations with these other drugs and underscores the importance of considering aspirin use in analyses of breast cancer survival.

[396]

**TÍTULO / TITLE:** - Novel Gene Expression Model for Outcome Prediction in Paediatric Medulloblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Mol Neurosci. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1007/s12031-013-0016-](#)

[6](#)

**AUTORES / AUTHORS:** - Zakrzewska M; Gresner SM; Zakrzewski K; Zalewska-Szewczyk B; Liberski PP

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Pathology and Neuropathology, Chair of Oncology, Medical University of Lodz, Czechoslowacka 8/10 str, 92-216, Lodz, Poland, [magdalena.zakrzewska@umed.lodz.pl](mailto:magdalena.zakrzewska@umed.lodz.pl).

**RESUMEN / SUMMARY:** - Medulloblastoma is the most frequent type of embryonal tumour in the paediatric population. The disease progression in patients with this tumour may be connected with the presence of stem/tumour-initiating cells, but the precise source and characteristics of such cells is still a subject of debate. Thus, we tried to analyse biomarkers for which a connection with the presence of stem/tumour-initiating cells was suggested. We evaluated the transcriptional level of the ATOH1, FUT4, NGFR, OTX1, OTX2, PROM1 and SOX1 genes in 48 samples of medulloblastoma and analysed their usefulness in the prediction of disease outcome. The analyses showed a strong correlation of PROM1, ATOH1 and OTX1 gene expression levels with the outcome ( $p \leq 0.2$ ). On the basis of the multivariate Cox regression analysis, we propose a three-gene model predicting risk of the disease, calculated as follows: [Formula: see text]. Survival analysis revealed a better outcome among standard-risk patients, with a 5-year survival rate of 65 %, compared to the 40 % rate observed among high-risk patients. The most promising advantage of such molecular analysis consists in the identification of molecular markers influencing clinical behaviour, which may in turn be useful in therapy optimization.

[397]

**TÍTULO / TITLE:** - Somatostatin receptor subtype 2 (sst) is a potential prognostic marker and a therapeutic target in medulloblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Childs Nerv Syst. 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1007/s00381-013-2142-](http://dx.doi.org/10.1007/s00381-013-2142-4)

[4](#)

**AUTORES / AUTHORS:** - Remke M; Hering E; Gerber NU; Kool M; Sturm D; Rickert CH; Gerss J; Schulz S; Hielscher T; Hasselblatt M; Jeibmann A; Hans V; Ramaswamy V; Taylor MD; Pietsch T; Rutkowski S; Korshunov A; Monoranu CM; Fruhwald MC

**INSTITUCIÓN / INSTITUTION:** - Division of Neurosurgery, Arthur and Sonia Labatt Brain Tumor Research Centre, Program in Developmental and Stem Cell Biology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

**RESUMEN / SUMMARY:** - INTRODUCTION: Neuroectodermal tumors in general demonstrate high and dense expression of the somatostatin receptor subtype 2 (sst2). It controls proliferation of both normal and neoplastic cells. sst2 has thus been suggested as a therapeutic target and prognostic marker for certain

malignancies. METHODS: To assess global expression patterns of sst 2 mRNA, we evaluated normal (n = 353) and tumor tissues (n = 340) derived from previously published gene expression profiling studies. These analyses demonstrated specific upregulation of sst 2 mRNA in medulloblastoma (p < 0.001). sst2 protein was investigated by immunohistochemistry in two independent cohorts. RESULTS: Correlation of sst2 protein expression with clinicopathological variables revealed significantly higher levels in medulloblastoma (p < 0.05) compared with CNS-PNET, ependymoma, or pilocytic astrocytoma. The non-SHH medulloblastoma subgroup tumors showed particularly high expression of sst2, when compared to other tumors and normal tissues. Furthermore, we detected a significant survival benefit in children with tumors exhibiting high sst2 expression (p = 0.02) in this screening set. A similar trend was observed in a validation cohort including 240 independent medulloblastoma samples. CONCLUSION: sst2 is highly expressed in medulloblastoma and deserves further evaluation in the setting of prospective trials, given its potential utility as a prognostic marker and a therapeutic target.

[398]

**TÍTULO / TITLE:** - Role of initial and day 4 human chorionic gonadotropin levels in predicting the outcome of single-dose methotrexate treatment in women with tubal ectopic pregnancy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Gynecol Obstet. 2013 May 12.

●●Enlace al texto completo (gratis o de pago) [1007/s00404-013-2879-](http://1007/s00404-013-2879-8)

[8](#)

**AUTORES / AUTHORS:** - Ustunyurt E; Duran M; Coskun E; Ustunyurt OB; Simsek H

**INSTITUCIÓN / INSTITUTION:** - The Department of Obstetrics and Gynecology, Bursa Sevket Yilmaz Research and Education Hospital, Bursa, Turkey, [dreminustunyurt@yahoo.com.tr](mailto:dreminustunyurt@yahoo.com.tr).

**RESUMEN / SUMMARY:** - PURPOSE: The purpose of this study was to evaluate the initial and day 4 beta-human chorionic gonadotropin (beta-hCG) levels as a predictor of methotrexate (MTX) therapy success for ectopic pregnancy. METHODS: Retrospective study of 87 patients with tubal ectopic pregnancy treated with a single dose of 50 mg/m<sup>2</sup> MTX at Bursa Sevket Yilmaz Research and Education Hospital between January 2011 and July 2012 was performed. RESULTS: The overall success rate is measured as 72.4 %. The two groups of patients, successfully treated patients (n = 63) and unsuccessfully treated patients (n = 24), were compared. The mean initial beta-hCG level was significantly lower in the treatment success group than in the treatment failure group (1,417 mIU/mL versus 5,995 mIU/mL, p < 0.001). The number of cases with decreasing beta-hCG level on day 4 was significantly more in the success group compared to the failure group (61.9 and 37.5 %, respectively, p = 0.04).

The success rate was 90 % when beta-hCG levels were <1,000 mIU/mL, 85.7 % when the levels were between 1,000 and 1,999 mIU/mL, and 76.5 % when the levels were between 2,000 and 2,999 mIU/mL, 54.5 % when the levels were between 3,000 and 3,999 mIU/mL. CONCLUSION: Single-dose MTX therapy is a safe and effective treatment modality for tubal ectopic pregnancies with the beta-hCG serum concentration below 3,000 mIU/mL, and beta-hCG level changes between days 0 and 4 after MTX therapy are important in predicting the outcome of treatment.

[399]

**TÍTULO / TITLE:** - Oral delivery of taurocholic acid linked heparin-docetaxel conjugates for cancer therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Control Release. 2013 May 9;170(1):74-82. doi: 10.1016/j.jconrel.2013.04.024.

●●Enlace al texto completo (gratis o de pago)

[1016/j.jconrel.2013.04.024](#)

**AUTORES / AUTHORS:** - Khatun Z; Nurunnabi M; Reeck GR; Cho KJ; Lee YK

**INSTITUCIÓN / INSTITUTION:** - Department of Chemical & Biological Engineering, Korea National University of Transportation, Chungju 380-702, Republic of Korea.

**RESUMEN / SUMMARY:** - We have synthesized taurocholic acid (TCA) linked heparin-docetaxel (DTX) conjugates for oral delivery of anticancer drug. The ternary biomolecular conjugates formed self-assembly nanoparticles where docetaxel was located inside the core and taurocholic acid was located on the surface of the nanoparticles. The coupled taurocholic acid in the nanoparticles had enhanced oral absorption, presumably through the stimulation of a bile acid transporter of the small intestine. The oral absorption profile demonstrated that the concentration of the conjugates in plasma is about 6 fold higher than heparin alone. An anti-tumor study in MDA-MB231 and KB tumor bearing mice showed significant tumor growth inhibition activity by the ternary biomolecular conjugates. Ki-67 histology study also showed evidence of anticancer activity of the nanoparticles. Finally, noninvasive imaging using a Kodak Molecular Imaging System demonstrated that the nanoparticles were accumulated efficiently in tumors. Thus, this approach for oral delivery using taurocholic acid in the ternary biomolecular conjugates is promising for treatment of various types of cancer.

[400]

**TÍTULO / TITLE:** - Influence of gefitinib and erlotinib on apoptosis and c-MYC expression in H23 lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1547-54.

**AUTORES / AUTHORS:** - Suenaga M; Yamamoto M; Tabata S; Itakura S; Miyata M; Hamasaki S; Furukawa T

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Gefitinib and erlotinib are inhibitors of epidermal growth factor receptor tyrosine kinase. The effects of these tyrosine kinase inhibitors on RAS-mutated cancer cells are unclear. **MATERIALS AND METHODS:** Influence of gefitinib and erlotinib treatment was examined in H23 adenocarcinoma and A431 epidermoid carcinoma cells. The WST-1 assay was performed for evaluating cell growth. The phosphorylation status of extracellular-signal-regulated kinases (ERK) and AKT (protein kinase B) was examined by western blot. Flow cytometry was used for analyzing cell-cycle status and apoptosis detection. **RESULTS:** In H23 cells, 20 µM erlotinib suppressed growth, while gefitinib did not suppress proliferation after 48 h of treatment. Neither gefitinib nor erlotinib affected the phosphorylation of ERK and AKT in H23 cells. Erlotinib augmented the sub-G1 population of H23 cells, while gefitinib reduced it. **CONCLUSION:** In H23 cells, erlotinib accelerated apoptosis, while gefitinib induced G1 arrest.

[401]

**TÍTULO / TITLE:** - Machine learning for predicting the response of breast cancer to neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Am Med Inform Assoc. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [1136/amiajnl-2012-001332](#)

**AUTORES / AUTHORS:** - Mani S; Chen Y; Li X; Arlinghaus L; Chakravarthy AB; Abramson V; Bhavne SR; Levy MA; Xu H; Yankeelov TE

**INSTITUCIÓN / INSTITUTION:** - Division of Translational Informatics, Department of Medicine, University of New Mexico, Albuquerque, New Mexico, USA.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To employ machine learning methods to predict the eventual therapeutic response of breast cancer patients after a single cycle of neoadjuvant chemotherapy (NAC). **MATERIALS AND METHODS:** Quantitative dynamic contrast-enhanced MRI and diffusion-weighted MRI data were acquired on 28 patients before and after one cycle of NAC. A total of 118 semiquantitative and quantitative parameters were derived from these data and combined with 11 clinical variables. We used Bayesian logistic regression in combination with feature selection using a machine learning framework for predictive model building. **RESULTS:** The best predictive models using feature selection obtained an area under the curve of 0.86 and an accuracy of 0.86, with a sensitivity of 0.88 and a specificity of 0.82.

DISCUSSION: With the numerous options for NAC available, development of a method to predict response early in the course of therapy is needed. Unfortunately, by the time most patients are found not to be responding, their disease may no longer be surgically resectable, and this situation could be avoided by the development of techniques to assess response earlier in the treatment regimen. The method outlined here is one possible solution to this important clinical problem. CONCLUSIONS: Predictive modeling approaches based on machine learning using readily available clinical and quantitative MRI data show promise in distinguishing breast cancer responders from non-responders after the first cycle of NAC.

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[402]

**TÍTULO / TITLE:** - Bcl-2 gene silence enhances the sensitivity toward 5-Fluorouracil in gastric adenocarcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Apr 3. pii: S0753-3322(13)00036-X. doi: 10.1016/j.biopha.2013.03.007.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2013.03.007](http://1016/j.biopha.2013.03.007)

**AUTORES / AUTHORS:** - Yu DF; Wu FR; Liu Y; Liu H; Xia Q

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Anhui, China. Electronic address: [ayfydf@163.com](mailto:ayfydf@163.com).

**RESUMEN / SUMMARY:** - Because of increased insensitivity or resistance to chemical treatment in tumor patients, specific apoptotic gene silence may provide a rational approach for the development of novel therapeutic strategies. This study was to investigate whether downregulation of Bcl-2 expression by small interfering RNA (siRNA) against the Bcl-2 gene would enhance the apoptosis and sensitivity of gastric adenocarcinoma SGC-7901 cell to 5-Fluorouracil. Transfections of SGC-7901 cells with siRNA were performed using cationic liposomes. Sequence-specific downregulation of Bcl-2 expression was measured by RT-PCR and Western blot analysis. Cell proliferation assay was determined by MTT assay and apoptotic cell rates were determined by flow cytometry assay. Results showed that the siRNA could downregulate Bcl-2 expression, which increased apoptosis and sensitivity of SGC-7901 cell to 5-Fluorouracil ( $P < 0.05$ ). This study indicated that inhibition of Bcl-2 expression by siRNA would be useful a new useful protocol to increase the effect of 5-Fluorouracil on treatment of gastric adenocarcinoma, which may play an important role in developing novel therapeutic strategies in the future.

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[403]

**TÍTULO / TITLE:** - Development of p21 Activated Kinase-targeted Multikinase Inhibitors that Inhibit Thyroid Cancer Cell Migration.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Endocrinol Metab. 2013 May 24.

●●Enlace al texto completo (gratis o de pago) [1210/jc.2012-3937](#)

**AUTORES / AUTHORS:** - Ma Y; McCarty SK; Kapuriya NP; Brendel VJ; Wang C; Zhang X; Jarjoura D; Saji M; Chen CS; Ringel MD

**INSTITUCIÓN / INSTITUTION:** - 1Division of Medicinal Chemistry, College of Pharmacy.

**RESUMEN / SUMMARY:** - Context:P21 activated kinases (PAKs) are a family of serine/threonine kinases that are downstream effectors of small GTPase Cdc42 and Rac. PAKs regulate cell motility, proliferation, and cytoskeletal rearrangement. PAK isoform expression and activity have been shown to be enhanced in cancer and to function as an oncogene in vivo. PAKs also have been implicated in cancer progression.Objective:In thyroid cancer we have previously determined that PAK overactivation is common in the invasive fronts of aggressive tumors and that it is functionally involved in thyroid cancer cell motility using molecular inhibitors. We report the development of two new PAK inhibiting compounds that were modified from the structure OSU-03012, a previously identified multi-kinase inhibitor that competitively blocks ATP binding of both phosphoinositide dependent kinase 1 (PDK1) and PAK1.Results:Seventeen compounds were created by combinatorial chemistry predicted to inhibit PAK activity with reduced anti-PDK1 effect. Two lead compounds were identified based the ability to inhibit PAK1 activity in an ATP-competitive manner without discernible in vivo PDK1 inhibitory activity in thyroid cancer cell lines. Both compounds reduced thyroid cancer cell viability. Although they are not PAK-specific on a multi-kinase screening assay, the anti-migration activity effect of the compounds in thyroid cancer cells was rescued by overexpression of a constitutively active PAK1, suggesting this activity is involved in this biological effect.Conclusions:We have developed two new multi-kinase inhibitors with anti-PAK activity that may serve as scaffolds for further compound development targeting this progression-related thyroid cancer target.

[404]

**TÍTULO / TITLE:** - Rank-based predictors for response and prognosis of neoadjuvant taxane-anthracycline-based chemotherapy in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):361-9. doi: 10.1007/s10549-013-2566-2. Epub 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2566-](#)

[2](#)

**AUTORES / AUTHORS:** - Zhang L; Hao C; Shen X; Hong G; Li H; Zhou X; Liu C; Guo Z

**INSTITUCIÓN / INSTITUTION:** - Bioinformatics Centre, School of Life Science, University of Electronic Science and Technology of China, Chengdu, 610054, China, [linzhang.bioinformatics@gmail.com](mailto:linzhang.bioinformatics@gmail.com).

**RESUMEN / SUMMARY:** - For neoadjuvant taxane and anthracycline-based chemotherapy for breast cancer, patients with pathological complete response (pCR) have a favorable prognosis compared with patients with residual disease (RD). Although a number of pCR predictors based on microarray profiles have been proposed to guide neoadjuvant chemotherapy, most of these have not been independently validated in inter-laboratory datasets, possibly owing to the fact that microarray measurements are sensitive to experimental batch effects and inter-array data normalizations. In this study, we developed a rank-based method to tackle this difficulty. First, we extracted from two datasets a combination of gene pairs, each of which had opposing relative expression orders in patients with pCR and those with RD, and used these to build a pCR predictor. This pCR predictor was found to have sensitivities of 74 and 86 % and specificities of 71 and 68 % in another two independent datasets from multiple laboratories, and these results were better than the performances of three previously reported predictors. Considering that patients with minimal RD also tend to have a good prognosis, we then developed a prognosis predictor for RD as a complement to the pCR predictor, in order to identify a group of patients likely to have a good prognosis, taking into account both the RD level and the intrinsic risk factors. In the independent validation, there was a significant difference ( $P = 0.001$ ) in distant relapse-free survival between the patients likely to and those not likely to have a good prognosis according to our prognosis predictor. In conclusion, the rank-based predictors for response and prognosis can accurately and robustly predict patients with improved prognosis who might benefit from neoadjuvant taxane and anthracycline-based chemotherapy.

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[405]

**TÍTULO / TITLE:** - Minireview: the molecular and genomic basis for prostate cancer health disparities.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Endocrinol. 2013 Jun;27(6):879-91. doi: 10.1210/me.2013-1039. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1210/me.2013-1039](http://1210/me.2013-1039)

**AUTORES / AUTHORS:** - Powell IJ; Bollig-Fischer A

**INSTITUCIÓN / INSTITUTION:** - 4201 Saint Antoine Street, UHC-7C, Detroit, Michigan 48201. [ipowell@med.wayne.edu](mailto:ipowell@med.wayne.edu).

**RESUMEN / SUMMARY:** - Despite more aggressive screening across all demographics and gradual declines in mortality related to prostate cancer (PCa)

in the United States, race disparities persist. For African American men (AAM), PCa is more often an aggressive disease showing increased metastases and greater PCa-related mortality compared with European American men. The earliest research points to how distinctions are likely the result of a combination of factors, including ancestry genetics and lifestyle variables. More recent research considers that cancer, although influenced by external forces, is ultimately a disease primarily driven by aberrations observed in the molecular genetics of the tumor. Research studying PCa predominantly from European American men shows that indolent and advanced or metastatic prostate tumors have distinguishing molecular genomic make-ups. Early yet increasing evidence suggests that clinically distinct PCa from AAM also display molecular distinctions. It is reasonable to predict that further study will reveal molecular subtypes and various frequencies for PCa subtypes among diverse patient groups, thereby providing insight as to the genomic lesions and gene signatures that are functionally implicated in carcinogenesis or aggressive PCa in AAM. That knowledge will prove useful in developing strategies to predict who will develop advanced PCa among AAM and will provide the rationale to develop effective individualized treatment strategies to overcome disparities.

[406]

**TÍTULO / TITLE:** - Gain-of-function microRNA screens identify miR-193a regulating proliferation and apoptosis in epithelial ovarian cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jun;42(6):1875-82. doi: 10.3892/ijo.2013.1896. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1896](#)

**AUTORES / AUTHORS:** - Nakano H; Yamada Y; Miyazawa T; Yoshida T

**INSTITUCIÓN / INSTITUTION:** - Biologics Research Laboratories, Kyowa Hakko Kirin Co., Ltd., Machida-shi, Tokyo 194-8533, Japan.

**RESUMEN / SUMMARY:** - MicroRNAs (miRNAs) are a small class of noncoding RNAs that negatively regulate gene expression, and are considered as new therapeutic targets for treating cancer. In this study, we performed a gain-of-function screen using miRNA mimic library (319 miRNA species) to identify those affecting cell proliferation in human epithelial ovarian cancer cells (A2780). We discovered a number of miRNAs that increased or decreased the cell viability of A2780 cells. Pro-proliferative and anti-proliferative miRNAs include oncogenic miR-372 and miR-373, and tumor suppressive miR-124a, miR-7, miR-192 and miR-193a, respectively. We found that overexpression of miR-124a, miR-192, miR-193a and miR193b inhibited BrdU incorporation in A2780 cells, indicating that these miRNAs affected the cell cycle. Overexpression of miR193a and miR-193b induced an activation of caspase 3/7, and resulted in apoptotic cell death in A2780 cells. A genomewide gene expression analysis with miR-193a-transfected A2780 cells led to identification

of ARHGAP19, CCND1, ERBB4, KRAS and MCL1 as potential miR-193a targets. We demonstrated that miR-193a decreased the amount of MCL1 protein by binding 3'UTR of its mRNA. Our study suggests the potential of miRNA screens to discover miRNAs as therapeutic tools to treat ovarian cancer.

[407]

**TÍTULO / TITLE:** - The Aurora Kinases Inhibitor VE-465 is a Novel Treatment for Glioblastoma Multiforme.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncology. 2013 Apr 27;84(6):326-335.

●●Enlace al texto completo (gratis o de pago) [1159/000347021](#)

**AUTORES / AUTHORS:** - Lee PY; Chen CL; Lin ZZ; Cheng AL; Chen EI; Whang-Peng J; Huang CY

**INSTITUCIÓN / INSTITUTION:** - Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC.

**RESUMEN / SUMMARY:** - Glioblastoma multiforme (GBM) is one of the most common and aggressive types of primary brain tumor. After complete surgical resection combined with radiation and chemotherapy, approximately 10% of patients survive for more than 5 years. Therefore, a novel therapy for GBM is needed. Aurora-A (AURKA) plays important roles in cell cycle regulation, such as centrosome maturation, chromatic separation, bipolar spindle assembly, and mitotic entry. To investigate the effects of AURKA inhibition, three GBM cell lines, including GBM 8401, GBM 8901, and U87-MG cells, were treated with the AURKA inhibitor VE-465. Sensitivities to VE-465, as indicated by 50% inhibitory concentration values for GBM 8401, GBM 8901, and U87-MG cells, were 6, 25, and 19 nM, respectively. Additionally, colony formation of GBM 8401 and GBM 8901 cells was decreased after treatment with the VE-465. VE-465 treatment increased polyploidy and p53 protein expression, and inhibited cell growth in a caspase-independent manner. Taken together, these results suggest that the inhibition of AURKA by a small-molecule inhibitor may have potential to serve as a novel therapeutic approach for GBM.

[408]

**TÍTULO / TITLE:** - DCE-MRI analysis methods for predicting the response of breast cancer to neoadjuvant chemotherapy: Pilot study findings.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Magn Reson Med. 2013 May 9. doi: 10.1002/mrm.24782.

●●Enlace al texto completo (gratis o de pago) [1002/mrm.24782](#)

**AUTORES / AUTHORS:** - Li X; Arlinghaus LR; Ayers GD; Chakravarthy AB; Abramson RG; Abramson VG; Atuegwu N; Farley J; Mayer IA; Kelley MC; Meszoely IM; Means-Powell J; Grau AM; Sanders M; Bhawe SR; Yankeelov TE

**INSTITUCIÓN / INSTITUTION:** - Vanderbilt University Institute of Imaging Science (VUIIS), Vanderbilt University, Nashville, Tennessee, USA.

**RESUMEN / SUMMARY:** - **PURPOSE:** The purpose of this pilot study is to determine (1) if early changes in both semiquantitative and quantitative DCE-MRI parameters, observed after the first cycle of neoadjuvant chemotherapy in breast cancer patients, show significant difference between responders and nonresponders and (2) if these parameters can be used as a prognostic indicator of the eventual response. **METHODS:** Twenty-eight patients were examined using DCE-MRI pre-, post-one cycle, and just prior to surgery. The semiquantitative parameters included longest dimension, tumor volume, initial area under the curve, and signal enhancement ratio related parameters, while quantitative parameters included  $K_{trans}$ ,  $v_e$ ,  $k_{ep}$ ,  $v_p$ , and  $\tau_{1\rho}$  estimated using the standard Tofts-Kety, extended Tofts-Kety, and fast exchange regime models. **RESULTS:** Our preliminary results indicated that the signal enhancement ratio washout volume and  $k_{ep}$  were significantly different between pathologic complete responders from nonresponders ( $P < 0.05$ ) after a single cycle of chemotherapy. Receiver operator characteristic analysis showed that the AUC of the signal enhancement ratio washout volume was 0.75, and the AUCs of  $k_{ep}$  estimated by three models were 0.78, 0.76, and 0.73, respectively. **CONCLUSION:** In summary, the signal enhancement ratio washout volume and  $k_{ep}$  appear to predict breast cancer response after one cycle of neoadjuvant chemotherapy. This observation should be confirmed with additional prospective studies. Magn Reson Med, 2013. © 2013 Wiley Periodicals, Inc.

[409]

**TÍTULO / TITLE:** - Discovery and synthesis of novel 4-aminopyrrolopyrimidine Tie-2 kinase inhibitors for the treatment of solid tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 May 15;23(10):3059-63. doi: 10.1016/j.bmcl.2013.03.012. Epub 2013 Mar 21.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.03.012](http://1016/j.bmcl.2013.03.012)

**AUTORES / AUTHORS:** - Arcari JT; Beebe JS; Berliner MA; Bernardo V; Boehm M; Borzillo GV; Clark T; Cohen BD; Connell RD; Frost HN; Gordon DA; Hungerford WM; Kakar SM; Kanter A; Keene NF; Knauth EA; Lagreca SD; Lu Y; Martinez-Alsina L; Marx MA; Morris J; Patel NC; Savage D; Soderstrom CI; Thompson C; Tkalcovic G; Tom NJ; Vajdos FF; Valentine JJ; Vincent PW; Wessel MD; Chen JM

**INSTITUCIÓN / INSTITUTION:** - Worldwide Research and Development, Pfizer Inc., Eastern Point Road, Groton, CT 06340, United States.

**RESUMEN / SUMMARY:** - The synthesis and biological evaluation of novel Tie-2 kinase inhibitors are presented. Based on the pyrrolopyrimidine chemotype, several new series are described, including the benzimidazole series by linking

a benzimidazole to the C5-position of the 4-amino-pyrrolopyrimidine core and the ketophenyl series synthesized by incorporating a ketophenyl group to the C5-position. Medicinal chemistry efforts led to potent Tie-2 inhibitors. Compound 15, a ketophenyl pyrrolopyrimidine urea analog with improved physicochemical properties, demonstrated favorable in vitro attributes as well as dose responsive and robust oral tumor growth inhibition in animal models.

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[410]

**TÍTULO / TITLE:** - Novel Hybrids of (Phenylsulfonyl)furoxan and Anilinopyrimidine as Potent and Selective Epidermal Growth Factor Receptor Inhibitors for Intervention of Non-Small-Cell Lung Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Chem. 2013 May 24.

●●Enlace al texto completo (gratis o de pago) [1021/jm400463q](http://1021/jm400463q)

**AUTORES / AUTHORS:** - Han C; Huang Z; Zheng C; Wan L; Zhang L; Peng S; Ding K; Ji H; Tian J; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Natural Medicines and double daggerCenter of Drug Discovery, China Pharmaceutical University , Nanjing 210009, People's Republic of China.

**RESUMEN / SUMMARY:** - A series of hybrids (12a-k) from (phenylsulfonyl)furoxan and anilinopyrimidine were synthesized and biologically evaluated as epidermal growth factor receptor (EGFR) inhibitors for intervention of non-small-cell lung cancer (NSCLC). Compound 12k exhibited strong and selective EGFR L858R/T790M inhibitory activity (IC<sub>50</sub> = 0.047 μM) and displayed antiproliferative effects on EGFR mutation NSCLC cell lines HCC827 (del E746\_A750) and H1975 (L858R/T790M) with IC<sub>50</sub> values of 0.007 and 0.029 μM, respectively. Additionally, 12k released high levels of NO in H1975 cells but not in normal human cells, and its activity was diminished by pretreatment with a NO scavenger. Furthermore, 12k induced apoptosis of H1975 and HCC827 cells more strongly than WZ4002 (1), inhibited EGFR downstream signaling in H1975 cells, and suppressed the nuclear factor-kappaB activation in H1975 cells, while 1 had no significant effects under the same conditions. Finally, 12k substantially inhibited tumor growth in an H1975 xenograft mouse model. Overall, 12k might be a promising candidate for the treatment of NSCLC.

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[411]

**TÍTULO / TITLE:** - Induction of DNA damage and ATF3 by retigeric acid B, a novel topoisomerase II inhibitor, promotes apoptosis in prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 May 18. pii: S0304-3835(13)00391-1. doi: 10.1016/j.canlet.2013.05.022.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.05.022](https://doi.org/10.1016/j.canlet.2013.05.022)

**AUTORES / AUTHORS:** - Liu Y; Gao F; Jiang H; Niu L; Bi Y; Young CY; Yuan H; Lou H

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Shandong University School of Medicine, Jinan 250012, China; Department of Natural Product Chemistry, Shandong University School of Pharmaceutical Sciences, Jinan 250012, China.

**RESUMEN / SUMMARY:** - Retigeric acid B (RB) has been reported to exhibit its anti-tumor activity in vitro and in vivo. Here, we found that RB significantly inhibited activity of topoisomerase IIalpha (Topo IIalpha), leading to remarkable DNA damage in prostate cancer (PCa) cells as evidenced by a strong induction of gammaH2AX and DNA fragmentation. Activation of ATM and ATR sequentially led to induction of phospho-Chk1/2 and phospho-Cdc25 in response to RB. Blockade of ATM/ATR signaling resulted in the attenuation of RB-induced gammaH2AX, and partially rescued RB-mediated cell death. RB treatment also resulted in inactivation of DNA repair proteins such as phospho-BRCA1, impairment of HR, and NHEJ repair as indicated by DNA end-joining assays. Meanwhile, a stress-responsive gene activating transcription factor 3 (ATF3) was noted for its predominant expression in response to RB-induced DNA damage. Knockdown of ATF3 inhibited the RB-induced up-regulation of cell cycle- and apoptosis-related genes such as DR5, DDIT4, CDC25A, GADD45A, and partially blocked RB-mediated inhibition on cell proliferation and induction of apoptosis, suggesting the crucial involvement of ATF3 in this event. Microarray data displayed that RB caused changes of genes required for damaged-DNA binding and repair, as well as ATF3 and its target genes. Our data firstly demonstrated that RB was a novel DNA Topo II inhibitor and triggered cell death by inducing DNA damage and stress-response, suggesting a promising anticancer agent.

[412]

**TÍTULO / TITLE:** - Predictors of recovery of ovarian function during aromatase inhibitor therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt149](https://doi.org/10.1093/annonc/mdt149)

**AUTORES / AUTHORS:** - Henry NL; Xia R; Banerjee M; Gersch C; McConnell D; Giacherio D; Schott AF; Pearlman M; Stearns V; Partridge AH; Hayes DF

**INSTITUCIÓN / INSTITUTION:** - Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor.

**RESUMEN / SUMMARY:** - BACKGROUND: Aromatase inhibitors (AIs) may cause a rise in estrogen levels due to ovarian function recovery in women with clinical chemotherapy-induced ovarian failure (CIOF). We carried out a prospective

registry trial to identify predictors of ovarian function recovery during AI therapy. PATIENTS AND METHODS: Women with hormone receptor (HR)-positive breast cancer who remained amenorrheic and had hormonal levels consistent with ovarian failure after adjuvant chemotherapy were enrolled in a multi-institutional clinical trial of anastrozole. Subjects underwent frequent assessment using an ultrasensitive estradiol assay. Multivariable analysis was used to evaluate clinical and biochemical predictors of ovarian function recovery within 48 weeks. RESULTS: Recovery of ovarian function during AI therapy was observed in 13 of 45 (28.9%) assessable subjects after a median 2.1 months (range 0.6-11.9). Median age at chemotherapy initiation was statistically significantly different between those who regained ovarian function (43 years, range 40-51) and those who remained postmenopausal (49 years, range 44-52;  $P < 0.0001$ ). CONCLUSIONS: A significant proportion of women with CIOF recover ovarian function during AI therapy, including a woman over age 50 at initiation of chemotherapy. Tamoxifen remains the standard of care for women with CIOF. If an AI is used, patients should be monitored frequently with high-quality estradiol assays. Clinicaltrials.gov: NCT00555477.

[413]

**TÍTULO / TITLE:** - Src homology phosphotyrosyl phosphatase-2 expression is an independent negative prognostic factor in human breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Histopathology. 2013 Mar 26. doi: 10.1111/his.12140.

●●Enlace al texto completo (gratis o de pago) [1111/his.12140](#)

**AUTORES / AUTHORS:** - Muenst S; Obermann EC; Gao F; Oertli D; Viehl CT; Weber WP; Fleming T; Gillanders WE; Soysal SD

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, University Hospital Basel, Basel, Switzerland; Department of Surgery, Washington University School of Medicine, St Louis, MO, USA.

**RESUMEN / SUMMARY:** - AIMS: Src homology phosphotyrosyl phosphatase-2 (SHP2) is a ubiquitously expressed phosphatase that plays an essential role in the downstream signalling pathways of multiple growth factor receptors, thus representing a potential target for cancer therapy. Recent studies suggest that SHP2 contributes to tumour initiation, progression and metastasis in breast cancer, yet the impact of SHP2 expression on prognosis in human breast cancer has not been evaluated. METHODS AND RESULTS: To explore further the role of SHP2 in breast cancer, we conducted an immunohistochemical study using a tissue microarray encompassing 1401 formalin-fixed breast cancer specimens with detailed clinical annotation and outcome data. Of 1401 evaluable breast cancers, 651 (46%) were positive for SHP2. SHP2 expression was associated positively with tumour grade, lymph node status and tumour stage. In univariate survival analysis, cases with SHP2 expression had a significantly worse overall survival (OS). In multivariate analysis, SHP2

remained an independent negative prognostic factor for OS. SHP2 expression was a negative prognostic factor for OS in the luminal A and the luminal B HER2- intrinsic subtypes. CONCLUSIONS: Our data demonstrate for the first time that SHP2 is an independent predictor of survival in breast cancer, suggesting that SHP2 may be a potential target for therapy.

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[414]

**TÍTULO / TITLE:** - EVI1 targets DeltaNp63 and upregulates the cyclin dependent kinase inhibitor p21 independent of p53 to delay cell cycle progression and cell proliferation in colon cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biochem Cell Biol. 2013 May 9. pii: S1357-2725(13)00137-4. doi: 10.1016/j.biocel.2013.04.032.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biocel.2013.04.032](http://1016/j.biocel.2013.04.032)

**AUTORES / AUTHORS:** - Nayak KB; Kuila N; Mohapatra AD; Panda AK; Chakraborty S

**INSTITUCIÓN / INSTITUTION:** - Department of Gene Function and Regulation, Institute of Life Sciences, Nalco Square, Bhubaneswar, Odisha, India.

**RESUMEN / SUMMARY:** - Several lines of evidence suggest that specific transcriptional events are involved in cell cycle, proliferation and differentiation processes; however, their deregulation by proto-oncogenes are involved in the development of leukemia and tumors. One such proto-oncogene is ecotropic viral integration site I which can differentially effect cell cycle progression and proliferation, in cell types of different origin. Our data for the first time shows that ecotropic viral integration site I binds to DeltaNp63 promoter element directly and down regulates its expression. Down regulation of DeltaNp63 induces the expression of p21 in HT-29 cells and also in colon carcinoma cells that do not express p53 including patient samples expressing low level of p53, that eventually delay cell cycle progression at G0/G1 phase. Concomitant silencing of ecotropic viral integration site I from the cells or introduction of DeltaNp63 to the cells significantly rescued this phenotype, indicating the growth defect induced by DeltaNp63 deficiency to be, at least in part, attributable to ecotropic viral integration site I function. The mutual regulation between ecotropic viral integration site I and DeltaNp63 may constitute a novel axis which might affect the downstream pathways in cells that do not express functional p53.

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[415]

**TÍTULO / TITLE:** - MACC1 mRNA Levels Predict Cancer Recurrence After Resection of Colorectal Cancer Liver Metastases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Surg. 2013 Jun;257(6):1089-95. doi: 10.1097/SLA.0b013e31828f96bc.

●●Enlace al texto completo (gratis o de pago)

[1097/SLA.0b013e31828f96bc](https://doi.org/10.1097/SLA.0b013e31828f96bc)

**AUTORES / AUTHORS:** - Isella C; Mellano A; Galimi F; Petti C; Capussotti L; De Simone M; Bertotti A; Medico E; Muratore A

**INSTITUCIÓN / INSTITUTION:** - \*Laboratory of Oncogenomics daggerDepartment of Surgical Oncology double daggerLaboratory of Molecular Pharmacology, IRC@C: Institute for Cancer Research at Candiolo, Italy section signDepartment of Oncology, University of Torino paragraph signDepartment of HPB and Digestive Surgery, Mauriziano Hospital, Torino, Italy.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** : Upon colon cancer metastasis resection in liver, disease outcome is heterogeneous, ranging from indolent to very aggressive, with early recurrence. The aim of this study is to investigate the capability of metastasis associated in colon cancer 1 (MACC1) levels measured in liver metastasis specimens to predict further recurrence of the disease. **METHODS:** : Gene expression and gene dosage of MACC1, hepatocyte growth factor (HGF), and hepatocyte growth factor receptor (MET) were assessed using quantitative realtime polymerase chain reaction on a cohort of 64 liver metastasis samples from patients with complete follow-up of 36 months and detailed clinical annotation. The most relevant mutations associated to prognosis in colorectal cancer, KRAS, and PIK3CA were assessed on the same specimens with Sanger sequencing. **RESULTS:** : Receiver operating characteristic (ROC) analysis revealed that MACC1 mRNA abundance is a good indicator of metastatic recurrence (AUC = 0.65, P < 0.05), whereas no such results were obtained with MET and HGF, nor with gene dosage. Generation of MACC1-based risk classes was capable of successfully separating patients into poor and good prognosis subgroups [hazard ratio (HR) = 5.236, 95% confidence interval (CI) = 1.2068-22.715, P < 0.05]. Also KRAS mutation was significantly associated with higher risk of recurrence (HR = 2.07, 95% CI = 1.048-4.09, P < 0.05). Cox regression multivariate analysis supported the independence of MACC1, but not KRAS, from known prognostic clinical information (Node Size HR = 3.155, 95% CI = 1.4418-6.905, P < 0.001, Preoperative carcinoembryonic antigen HR = 2.359, 95% CI = 1.0203-5.452, P < 0.05, MACC1 HR = 7.2739, 95% CI = 1.6584-31.905, P < 0.01). **CONCLUSIONS:** : MACC1, a new easily detectable biomarker in cancer, is an independent prognostic factor of recurrence after liver resection of colorectal cancer metastasis.

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[416]

**TÍTULO / TITLE:** - RNA interference-mediated knockdown of Livin suppresses cell proliferation and invasion and enhances the chemosensitivity to cisplatin in human osteosarcoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):159-68. doi: 10.3892/ijo.2013.1925. Epub 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1925](#)

**AUTORES / AUTHORS:** - Li X; Fan S; Li L; Wang L; Fan G; Zhao Q; Li Y

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopaedic Surgery, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, P.R. China.

**RESUMEN / SUMMARY:** - Livin is a novel member of the inhibitor of apoptosis protein (IAP) family that has been reported to be overexpressed in a variety of human malignancies, including osteosarcoma. However, the potential roles of Livin in tumorigenesis have not been elucidated. In the present study, we employed RNA interference (RNAi) technology to suppress endogenous Livin expression in osteosarcoma cells and successfully generated a U2-OS cell line with stably knockdown of Livin. Functional analysis showed that knockdown of Livin significantly reduced cell proliferation, colony formation, and invasion and migration capacities of U2-OS cells in vitro. Moreover, specific downregulation of Livin led to cell cycle arrest at the G0/G1 phase and eventual apoptosis. Meanwhile, western blot analysis revealed that cells with stably knockdown of Livin showed decreased expression levels of Cyclin D1, Bcl-2, matrix metalloproteinase (MMP)-2 and MMP-9, but increased expression levels of activated Caspase-3, Bax and cleaved poly (ADP-ribose) polymerase (PARP) compared to those transfected with a control vector. We also observed that suppression of Livin expression in osteosarcoma cells increased their chemosensitivity to cisplatin. Taken together, our data suggest that Livin is involved in tumorigenesis of human osteosarcoma and may serve as a promising therapeutic target for osteosarcoma.

[417]

**TÍTULO / TITLE:** - Cytoprotective role of autophagy during paclitaxel-induced apoptosis in Saos-2 osteosarcoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jun;42(6):1985-92. doi: 10.3892/ijo.2013.1884. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1884](#)

**AUTORES / AUTHORS:** - Kim HJ; Lee SG; Kim YJ; Park JE; Lee KY; Yoo YH; Kim JM

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopaedic Surgery, College of Medicine, Dong-A University, Busan 602-714, Republic of Korea.

**RESUMEN / SUMMARY:** - Osteosarcoma (OS) is the most common primary malignant bone cancer in children and adolescents. Although paclitaxel (PCX) has been considered one of the most important cancer chemotherapeutic drugs, the current protocols for OS treatment do not incorporate this agent.

Therefore, the purpose of this study was to evaluate the induction of cell death in OS cells after exposure to PCX, to identify the cell death mechanism(s) activated by PCX and to investigate whether autophagy is associated with PCX-induced apoptosis. The results of the present study confirmed that exposure to low PCX concentrations can induce apoptotic cell death in Saos-2 cells; furthermore, caspase-3 activation, PARP degradation and XIAP downregulation were observed in combination with PCX-induced apoptosis. The potential involvement of mitochondrial events (intrinsic apoptotic pathway) in PCX-induced apoptosis in OS cells was verified by the alteration (depolarization) of mitochondrial membrane potential. In addition, pretreatment with 3-methyladenine (3-MA), a specific inhibitor of autophagy, significantly increased PCX-induced apoptotic cell death in Saos-2 cells. The augmentation of PCX-induced apoptosis by 3-MA was accompanied by increase in the cytochrome c release from the mitochondria, caspase-3 activity and XIAP downregulation, which suggests that inhibiting autophagy further stimulates the PCX-induced mitochondrion-related (intrinsic) apoptotic pathway by provoking caspase-3 activation. Thus, autophagy observed during PCX-induced apoptosis in Saos-2 OS cells represents the role of cytoprotection in cellular homeostatic processes. In conclusion, the results of this study revealed that PCX exposure effectively induces OS cell death by apoptosis associated with the mitochondrial-mediated caspase-dependent pathway. PCX can increase autophagic activity and suppressing autophagy enhances PCX-induced apoptosis in OS cells. Therefore, it is suggested that combination treatment involving low-dose PCX therapy and autophagy inhibitor therapy could be an effective and potent strategy for improved chemotherapy for OS in the near future.

[418]

**TÍTULO / TITLE:** - Genistein induces G2/M cell cycle arrest and apoptosis via ATM/p53-dependent pathway in human colon cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):289-96. doi: 10.3892/ijo.2013.1946. Epub 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1946](#)

**AUTORES / AUTHORS:** - Zhang Z; Wang CZ; Du GJ; Qi LW; Calway T; He TC; Du W; Yuan CS

**INSTITUCIÓN / INSTITUTION:** - Tang Center for Herbal Medicine Research, University of Chicago, Chicago, IL 60637, USA.

**RESUMEN / SUMMARY:** - Soybean isoflavones have been used as a potential preventive agent in anticancer research for many years. Genistein is one of the most active flavonoids in soybeans. Accumulating evidence suggests that genistein alters a variety of biological processes in estrogen-related malignancies, such as breast and prostate cancers. However, the molecular

mechanism of genistein in the prevention of human colon cancer remains unclear. Here we attempted to elucidate the anticarcinogenic mechanism of genistein in human colon cancer cells. First we evaluated the growth inhibitory effect of genistein and two other isoflavones, daidzein and biochanin A, on HCT-116 and SW-480 human colon cancer cells. In addition, flow cytometry was performed to observe the morphological changes in HCT-116/SW-480 cells undergoing apoptosis or cell cycle arrest, which had been visualized using Annexin V-FITC and/or propidium iodide staining. Real-time PCR and western blot analyses were also employed to study the changes in expression of several important genes associated with cell cycle regulation. Our data showed that genistein, daidzein and biochanin A exhibited growth inhibitory effects on HCT-116/SW-480 colon cancer cells and promoted apoptosis. Genistein showed a significantly greater effect than the other two compounds, in a time- and dose-dependent manner. In addition, genistein caused cell cycle arrest in the G2/M phase, which was accompanied by activation of ATM/p53, p21waf1/cip1 and GADD45alpha as well as downregulation of cdc2 and cdc25A demonstrated by q-PCR and immunoblotting assay. Interestingly, genistein induced G2/M cell cycle arrest in a p53-dependent manner. These findings exemplify that isoflavones, especially genistein, could promote colon cancer cell growth inhibition and facilitate apoptosis and cell cycle arrest in the G2/M phase. The ATM/p53-p21 cross-regulatory network may play a crucial role in mediating the anticarcinogenic activities of genistein in colon cancer.

[419]

**TÍTULO / TITLE:** - Antiproliferative activity of 2,3-disubstituted indoles toward apoptosis-resistant cancers cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Jun 1;23(11):3277-82. doi: 10.1016/j.bmcl.2013.03.110. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.03.110](#)

**AUTORES / AUTHORS:** - Magedov IV; Lefranc F; Frolova LV; Banuls LM; Peretti AS; Rogelj S; Mathieu V; Kiss R; Kornienko A

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, New Mexico Institute of Mining and Technology, Socorro, NM 87801, USA. Electronic address: [imagedov@nmt.edu](mailto:imagedov@nmt.edu).

**RESUMEN / SUMMARY:** - Many types of cancer, including glioma, melanoma, NSCLC, among others, are resistant to apoptosis induction and poorly responsive to current therapies with proapoptotic agents. We describe a series of 2,3-disubstituted indoles, which display cytostatic rather than cytotoxic effects in cancer cells, and serve as a new chemical scaffold to develop anticancer agents capable of combating apoptosis-resistant cancers associated with dismal prognoses.

[420]

**TÍTULO / TITLE:** - Synergistic induction of apoptosis by sulindac and simvastatin in A549 human lung cancer cells via reactive oxygen species-dependent mitochondrial dysfunction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):262-70. doi: 10.3892/ijo.2013.1933. Epub 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1933](#)

**AUTORES / AUTHORS:** - Hwang KE; Park C; Kwon SJ; Kim YS; Park DS; Lee MK; Kim BR; Park SH; Yoon KH; Jeong ET; Kim HR

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Institute of Wonkwang Medical Science, Wonkwang University, School of Medicine, Iksan, Jeonbuk 570-749, Republic of Korea.

**RESUMEN / SUMMARY:** - Prevention of lung cancer is more feasible and holds greater promise when different agents are used in combination to target multiple processes during carcinogenesis. The mechanisms by which non-steroidal anti-inflammatory drugs and statins inhibit cancer cell growth and induce apoptosis are not fully understood. This study was designed to investigate lung cancer chemoprevention through a mechanism-based approach using sulindac at low doses in combination with simvastatin. We found that sulindac-induced cytotoxicity was significantly enhanced in the presence of simvastatin. The combination of sulindac and simvastatin induced more extensive caspase-dependent apoptosis in A549 cells compared to that induced with either drug alone. The combination of sulindac and simvastatin also increased the loss of mitochondrial transmembrane potential (P<sub>sim</sub>) and the cytosolic release of cytochrome c. In addition, ROS generation in cells treated with both sulindac and simvastatin was markedly increased compared to cells treated with either sulindac or simvastatin alone. The enhancement of ROS generation by sulindac and simvastatin was abrogated by pretreatment with NAC, which also prevented apoptosis and mitochondrial dysfunction induced by sulindac and simvastatin. These results suggest that sulindac and simvastatin-induced ROS generation in A549 lung cancer cells causes their accumulation in mitochondria, triggering the release of apoptogenic molecules from the mitochondria to the cytosol, and thus leading to caspase activation and cell death.

[421]

**TÍTULO / TITLE:** - A novel trifluoromethyl benzopyran induces G1 cell cycle arrest and apoptosis in HeLa human cervical carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 May 24. doi: 10.3892/ijo.2013.1958.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1958](#)

**AUTORES / AUTHORS:** - Zhang X; Hwang J; Jia X; Shin DS; You S; Kim DK

**INSTITUCIÓN / INSTITUTION:** - Shenyang Pharmaceutical University, Shenyang 110016, P.R. China.

**RESUMEN / SUMMARY:** - In the present study, a biologically active 4-(trifluoromethyl)phenyl piperazin moiety was linked to a 2,2-dimethyl-2H-benzopyran template to generate (3R,4S)-2,2-dimethyl-6-nitro-4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl) chroman-3-ol (C110g), and the cellular and molecular mechanisms by which C110g exerts cytotoxic effects on the HeLa human cervical cancer cell line were further investigated. C110g suppressed the viability of HeLa cells in both concentration- and time-dependent manner (IC<sub>50</sub> of 17 µM) by inducing DNA damage and G1 cell cycle arrest. Characteristic changes in nuclear morphology and Annexin V/PI staining pointed to apoptosis as the mode of cell death. The levels of p53 and p21 were increased in the C110g-treated cells, with a corresponding increase in Bax/Bcl-2 protein ratio. Subsequently, C110g induced the cytoplasmic release of cytochrome c from the mitochondria accompanied by a decreased mitochondrial membrane potential and activation of caspase-3 and -9. These results confirmed that the C110g transduced the apoptotic signal via the mitochondrial pathway. Caspase-8, typically associated with the initiation of the death receptor pathway, was activated, suggesting the extrinsic pathway might also be involved. However, C110g did not result in reactive oxygen species (ROS) generation. Taken together, these findings indicate that the DNA damage-dependent p53-regulated mitochondrial pathway as well as the extrinsic pathway play a crucial role in C110g-induced apoptosis, which provide a better understanding of the molecular mechanisms of trifluoromethyl benzopyrans in cervical cancer.

[422]

**TÍTULO / TITLE:** - FGF Receptors: Cancer Biology and Therapeutics.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Res Rev. 2013 May 21. doi: 10.1002/med.21288.

●●Enlace al texto completo (gratis o de pago) [1002/med.21288](#)

**AUTORES / AUTHORS:** - Katoh M; Nakagama H

**INSTITUCIÓN / INSTITUTION:** - Division of Integrative Omics and Bioinformatics, National Cancer Center, 5-1-1 Tsukiji, Chuo Ward, Tokyo, 104-0045, Japan.

**RESUMEN / SUMMARY:** - Fibroblast growth factors (FGFs) are involved in a variety of cellular processes, such as stemness, proliferation, anti-apoptosis, drug resistance, and angiogenesis. Here, FGF signaling network, cancer genetics/genomics of FGF receptors (FGFRs), and FGFR-targeted therapeutics will be reviewed. FGF signaling to RAS-MAPK branch and canonical WNT signaling cascade mutually regulate transcription programming. FGF signaling to PI3K-AKT branch and Hedgehog, Notch, TGFβ, and noncanonical WNT signaling cascades regulate epithelial-to-mesenchymal transition (EMT) and invasion. Gene amplification of FGFR1 occurs in lung cancer and estrogen

receptor (ER)-positive breast cancer, and that of FGFR2 in diffuse-type gastric cancer and triple-negative breast cancer. Chromosomal translocation of FGFR1 occurs in the 8p11 myeloproliferative syndrome and alveolar rhabdomyosarcoma, as with FGFR3 in multiple myeloma and peripheral T-cell lymphoma. FGFR1 and FGFR3 genes are fused to neighboring TACC1 and TACC3 genes, respectively, due to interstitial deletions in glioblastoma multiforme. Missense mutations of FGFR2 are found in endometrial uterine cancer and melanoma, and similar FGFR3 mutations in invasive bladder tumors, and FGFR4 mutations in rhabdomyosarcoma. Dovitinib, Ki23057, ponatinib, and AZD4547 are orally bioavailable FGFR inhibitors, which have demonstrated striking effects in preclinical model experiments. Dovitinib, ponatinib, and AZD4547 are currently in clinical trial as anticancer drugs. Because there are multiple mechanisms of actions for FGFR inhibitors to overcome drug resistance, FGFR-targeted therapy is a promising strategy for the treatment of refractory cancer. Whole exome/transcriptome sequencing will be introduced to the clinical laboratory as the companion diagnostic platform facilitating patient selection for FGFR-targeted therapeutics in the era of personalized medicine.

[423]

**TÍTULO / TITLE:** - Curcumin induces apoptosis in human colorectal carcinoma (HCT-15) cells by regulating expression of Prp4 and p53.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cells. 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1007/s10059-013-0038-](#)

[5](#)

**AUTORES / AUTHORS:** - Shehzad A; Lee J; Huh TL; Lee YS

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, College of Natural Sciences, Kyungpook National University, Daegu, 700-721, Korea.

**RESUMEN / SUMMARY:** - Curcumin (diferuloylmethane), the yellow pigment of turmeric, is one of the most commonly used and extensively studied phytochemicals due to its pleiotropic effects in several human cancers. In the current study, the therapeutic efficacy of curcumin was investigated in human colorectal carcinoma HCT-15 cells. Curcumin inhibited HCT-15 cells proliferation and induced apoptosis in a dose- and time-dependent manner. Hoechst 33342 and DCFHDA staining revealed morphological and biochemical features of apoptosis as well as ROS generation in HCT-15 cells treated with 30 and 50 μM curcumin. Over-expression of pre-mRNA processing factor 4B (Prp4B) and p53 mutations have been reported as hallmarks of cancer cells. Western blot analysis revealed that curcumin treatment activated caspase-3 and decreased expression of p53 and Prp4B in a time-dependent manner. Transfection of HCT-15 cells with Prp4B clone perturbed the growth inhibition induced by 30 μM curcumin. Fractionation of cells revealed increased

accumulation of Prp4B in the nucleus, following its translocation from the cytoplasm. To further evaluate the underlying mechanism and survival effect of Prp4B, we generated siRNA-Prp4B HCT15 clones. Knockdown of Prp4B with siRNA diminished the protective effects of Prp4B against curcumin-induced apoptosis. These results suggest a possible underlying molecular mechanism in which Prp4B over-expression and activity are closely associated with the survival and regulation of apoptotic events in human colon cancer HCT-15 cells.

[424]

**TÍTULO / TITLE:** - Notch3 induces epithelial-mesenchymal transition and attenuates carboplatin-induced apoptosis in ovarian cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Mar 29. pii: S0090-8258(13)00174-1. doi: 10.1016/j.ygyno.2013.03.019.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.03.019](#)

**AUTORES / AUTHORS:** - Gupta N; Xu Z; El-Sehemy A; Steed H; Fu Y

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada; Department of Oncology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Notch3 is implicated in chemoresistance of ovarian cancer, yet the molecular mechanism underlying Notch3-mediated drug resistance remains to be elucidated. Here, we investigated the role of Notch3 in carboplatin-induced apoptosis in ovarian cancer cells. **METHODS:** Ovarian cancer cell line OVCA429 cells were stably transduced with an empty vector or a retroviral vector expressing the Notch3 intracellular domain (NICD3, the constitutively active form of Notch3) to generate OVCA429/vector and OVCA429/NICD3 cells. Epithelial-mesenchymal transition (EMT) was determined by morphological change and expression of the EMT markers. Carboplatin-induced cytotoxicity was determined by the neutral red uptake assay. Apoptosis was determined by Annexin V staining and Western blotting. Carboplatin-induced phosphorylation of extracellular signal-regulated kinase (ERK) was identified by a phospho-kinase array and confirmed by Western blotting. **RESULTS:** Activation of Notch3 in OVCA429 cells causes a spindle and fibroblast-like morphology, induces the expression of smooth muscle alpha-actin, Slug and Snail, but decreases the expression of E-cadherin, indicating that Notch3 activation induces EMT in OVCA429 cells. Furthermore, Notch3 activation renders OVCA429 cells more resistant to carboplatin-induced cytotoxicity and attenuates carboplatin-induced apoptosis in these cells. Our results indicate that phosphorylation of ERK is a positive regulator of carboplatin-induced apoptosis in OVCA429 cells. Interestingly, carboplatin-induced ERK phosphorylation is inhibited by Notch3 activation.

CONCLUSIONS: Notch3 activation induces EMT and attenuates carboplatin-induced apoptosis in OVCA429 cells. ERK phosphorylation plays a pro-apoptotic role in carboplatin-induced apoptosis in OVCA429 cells. Interestingly, Notch3 activation attenuates carboplatin-induced ERK phosphorylation in these cells.

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[425]

**TÍTULO / TITLE:** - Tissue expression of MLH1, PMS2, MSH2, and MSH6 proteins and prognostic value of microsatellite instability in Wilms tumor: experience of 45 cases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Pediatr Hematol Oncol.* 2013 May;30(4):273-84.

●●Enlace al texto completo (gratis o de pago)

[3109/08880018.2013.780274](#)

**AUTORES / AUTHORS:** - Diniz G; Aktas S; Cubuk C; Ortac R; Vergin C; Olgun N

**INSTITUCIÓN / INSTITUTION:** - DEU Oncology Institute, Dr. Behcet Uz Children's Hospital, Pathology, Izmir, Turkey. [agdiniz@gmail.com](mailto:agdiniz@gmail.com)

**RESUMEN / SUMMARY:** - BACKGROUND: Although the importance of microsatellite instability (MSI) and mismatch repair genes (MMR) is strongly established in colorectal cancer seen in the Lynch syndrome, its significance has not been fully established in Wilms tumor (WT). The aim of this study was to determine the prognostic value of MSI and MMR proteins in WT. METHODS: This study included 45 pediatric cases with nephroblastoma. Protein expression was analyzed by immunohistochemistry of archival tissue sections. Real-time PCR melting analysis and fluorescence capillary electrophoresis (FCE) were performed to evaluate the MSI markers BAT25, BAT26, NR21, NR24, MONO27, penta D, and penta C in DNA extracted from tumor and normal tissues. RESULTS: Lower levels of MSI were observed in six cases (13.3%). There were no statistically significant correlations between MSI and some clinical prognostic factors such as stage of the tumors, and survival rates. Nineteen tumors (42.2%) showed loss of protein expression of MLH1, PMS2, MSH2, or MSH6. MMR protein defects were correlated with size ( $P = .021$ ), and stage ( $P = .019$ ) of the tumor, and survival rates ( $P < .01$ ). Similarly MSI was also correlated with the size of the tumor ( $P = .046$ ). CONCLUSIONS: This study showed that a small proportion of WT might be associated with the presence of MSI, as is the case with defects of DNA mismatch repair genes in the pathogenesis of WT. However, there was no concordance with the frequency of tissue expression of MMR proteins and MSI. These findings suggest that MMR genes may play an important role in the development of WT via different pathways.

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[426]

**TÍTULO / TITLE:** - Glycyrrhiza polysaccharide induces apoptosis and inhibits proliferation of human hepatocellular carcinoma cells by blocking PI3K/AKT signal pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Jun;34(3):1381-9. doi: 10.1007/s13277-013-0746-7. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0746-](#)

[7](#)

**AUTORES / AUTHORS:** - Chen J; Jin X; Chen J; Liu C

**INSTITUCIÓN / INSTITUTION:** - Medical School of Taizhou University, Taizhou, Zhejiang, 318000, China, [chenyujia10@163.com](mailto:chenyujia10@163.com).

**RESUMEN / SUMMARY:** - To study the antitumor effect of glycyrrhiza polysaccharide (GPS) on human hepatocellular carcinoma cells and its mechanism, GPS was extracted and identified with phenol-sulfuric acid assay, Limulus amoebocytes lysate assay, gel permeation chromatography, and infrared spectroscopy analysis. To study its antitumor function, 4-5-week-old imprinting control region mice were subcutaneously implanted with H22 cells and intragastrically subjected to 1 ml GPS (25, 50, and 75 mg/kg/day), 150 mg/kg cyclophosphamide in a dose of 150 mg/kg, or equal volume of phosphate buffered saline as control. Tumor weights were detected 10 days later. Apoptosis of intraperitoneally cultured and GPS-treated H22 cells was identified by flow cytometry and 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolyl-carbocyanine iodide. In vitro, the function of GPS on cell proliferation was applied on BEL7402 cells and confirmed by 4,6-diamidino-2-phenylindole staining. Assessment of the effect of GPS on P53 gene was analyzed by real-time PCR and Western blot, and the effects of GPS on phosphatidylinositol-3 kinase (PI3K), AKT, p-PI3K, and p-AKT were analyzed by Western blot. We extracted the GPS, and it dose-dependently inhibited the tumorigenicity of hepatocellular carcinoma cells in nude mice. GPS treatment resulted in a significant ( $P < 0.05$ ) dose-dependent increase in the number of apoptotic cells in vivo and a significant ( $P < 0.05$ ) dose-dependent decrease in hepatocellular carcinoma cell proliferation in vitro. GPS modified multiple key enzymes (p-PI3K, p-AKT, and P53) in P53/PI3K/AKT signaling pathways on DNA or protein levels. Taken together, we extracted the GPS successfully and our findings suggest that GPS functions as a tumor suppressor through influencing the P53/PI3K/AKT pathway in the carcinogenesis of hepatocellular carcinoma and may have therapeutic implications for the clinical management of hepatocellular carcinoma patients.

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[427]

**TÍTULO / TITLE:** - Improved detection rate of cytogenetic abnormalities in chronic lymphocytic leukemia and other mature B-cell neoplasms with use of CpG-oligonucleotide DSP30 and interleukin 2 stimulation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Clin Pathol. 2013 May;139(5):662-9. doi: 10.1309/AJCP7G4VMYZJQVFI.

●●Enlace al texto completo (gratis o de pago)

[1309/AJCP7G4VMYZJQVFI](#)

**AUTORES / AUTHORS:** - Shi M; Cipollini MJ; Crowley-Bish PA; Higgins AW; Yu H; Miron PM

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, UMASS Memorial Medical Center, Worcester, MA 01605, USA.

**RESUMEN / SUMMARY:** - Detection of cytogenetic abnormalities requires successful culture of the clonal population to obtain metaphase chromosomes for study, and as such, has been hampered by low mitotic indices of mature B cells in culture. Our study presents data on the improved abnormality detection rate with the use of a CpG-oligonucleotide/interleukin 2 (OL/IL-2) culture protocol for mature B-cell neoplasms, including chronic lymphocytic leukemia (CLL) and non-CLL specimens. The increased detection rate of abnormalities, compared with unstimulated culture and traditional pokeweed mitogen culture, was statistically significant for both CLL and non-CLL neoplasms. For CLL specimens, our data also showed that for cytogenetically visible aberrations, OL/IL-2 was as, if not more, sensitive than detection with interphase fluorescence in situ hybridization (iFISH). Use of OL/IL-2 allowed a number of abnormalities to be detected, which were not covered by specific iFISH panels, especially balanced translocations. Therefore, OL/IL-2 stimulation improves diagnostic sensitivity and increases discovery rate of novel prognostic findings.

[428]

**TÍTULO / TITLE:** - Ericifolin: a novel antitumor compound from allspice that silences androgen receptor in prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bqt123](#)

**AUTORES / AUTHORS:** - Shamaladevi N; Lyn DA; Shaaban KA; Zhang L; Villate S; Rohr J; Lokeshwar BL

**INSTITUCIÓN / INSTITUTION:** - Department of Urology and.

**RESUMEN / SUMMARY:** - Silencing of androgen receptor (AR) signaling is a specific and effective mechanism to cure cancer of the prostate (CaP). In this study, the isolation and characterization of a compound from the aromatic berries of Pimenta dioica (allspice) that silences AR is presented. Potential antitumor activities of an aqueous allspice extract (AAE) and a compound purified from the extract were tested on CaP cells. AAE inhibited tumor cell proliferation and colony formation (50% growth inhibition approximately 40-85 microg/ml) but not the viability of quiescent normal fibroblasts or non-tumorigenic prostate cells. In tumor cells, AAE inhibited cell cycle progression at

G1/S, induced apoptosis or autophagy. Apoptosis was by caspase-dependent poly (ADP ribose) polymerase cleavage. A caspase-independent, apoptosis-inducing factor-mediated mechanism of apoptosis caused cell death in castration-resistant AR-positive or AR-negative CaP cells, such as CWR22RV1, PC-3 or DU145 cells. Treatment with AAE decreased the levels of AR messenger RNA (mRNA), protein and silenced AR activity in AR-positive cells. AR depletion was due to inhibition of AR promoter activity and mRNA stability. Delayed tumor growth (~55%) without measurable systemic toxicity was observed in LNCaP tumor-bearing mice treated with AAE by oral or intraperitoneal routes. LNCaP tumor tissues from AAE-treated mice revealed increased apoptosis as a potential mechanism of antitumor activity of AAE. The chemical identity of bioactive compound in AAE was established through multistep high-performance liquid chromatography fractionation, mass and Nuclear Magnetic Resonance spectroscopies. The compound, eugenol 5-O-beta-(6'-galloyl)glucopyranoside) or ericifolin (EF), showed antiproliferative, pro-apoptosis and anti-AR transcription activities. These results demonstrate a potential use of AAE and EF against prostate cancer.

[429]

**TÍTULO / TITLE:** - Knockdown of the Bcl-2 gene increases sensitivity to EGFR tyrosine kinase inhibitors in the H1975 lung cancer cell line harboring T790M mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jun;42(6):2094-102. doi: 10.3892/ijo.2013.1895. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1895](#)

**AUTORES / AUTHORS:** - Zou M; Xia S; Zhuang L; Han N; Chu Q; Chao T; Peng P; Chen Y; Gui Q; Yu S

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, P.R. China.

**RESUMEN / SUMMARY:** - Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are being widely used as targeted therapy in non-small cell lung cancer (NSCLC), but most cases acquire drug-resistance in 9 months. However, the mechanisms of resistance are still not fully understood. Since it has been demonstrated that EGFR-TKI-mediated repression of downstream signaling cascades and apoptosis induction is a key mechanism through which EGFR-TKIs exert their cytotoxic effects, we reasoned that activation of downstream signaling pathways and changes in the expression of apoptosis-related proteins contribute to the acquired resistance to EGFR-TKIs. We analyzed the protein levels of p-Akt, Bcl-2, Bax between gefitinib-sensitive and gefitinib-resistant lung cancer cell lines and evaluated whether targeting the anti-apoptotic protein Bcl-2 induces cell apoptosis and further sensitizes

resistant H1975 cells to gefitinib. The data showed that p-Akt was activated and accompanied by substantial Bcl-2 in the H1975 lung cancer cell line, whereas no evidence was observed in HCC827 cells. Using small interfering RNA (siRNA) to silence Bcl-2 in H1975 cells led to significant downregulation of Bcl-2 protein expression, decreased cell viability in vitro and induced intrinsic apoptosis confirmed by flow cytometry and PARP cleavage. In Bcl-2 siRNA-transfected cells, adding gefitinib further reduced the number of viable cells, induced apoptosis to a greater extent compared to either treatment alone. These preclinical data suggested that downregulation of Bcl-2 by RNAi in the gefitinib-resistant H1975 lung cancer cell line with T790M mutation enhanced the effects of gefitinib and may offer a novel therapeutic strategy for the treatment of NSCLC.

[430]

**TÍTULO / TITLE:** - Clinicopathological and prognostic significance of galectin-1 and vascular endothelial growth factor expression in gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Gastroenterol. 2013 Apr 7;19(13):2073-9. doi: 10.3748/wjg.v19.i13.2073.

●●Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i13.2073](#)

**AUTORES / AUTHORS:** - Chen J; Zhou SJ; Zhang Y; Zhang GQ; Zha TZ; Feng YZ; Zhang K

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Yixing People's Hospital, the Affiliated Hospital of Jiangsu University, Yixing 214200, Jiangsu Province, China.

**RESUMEN / SUMMARY:** - AIM: To evaluate the expression of galectin-1 and vascular endothelial growth factor (VEGF) in gastric cancer and investigate their relationships with clinicopathologic factors and prognostic significance. METHODS: Galectin-1 and VEGF were immunohistochemically investigated in tumor samples obtained from 214 gastric cancer patients with all tumor stages. Immunohistochemical analyses for galectin-1 and VEGF expression were performed on formalin-fixed, paraffin-embedded sections of surgical specimens. The relationship between the expression and staining intensity of galectin-1 and VEGF, clinicopathologic variables, and patient survival were analyzed. All patients underwent follow-up until cancer-related death or more than five years after tumor resection. P values < 0.05 were considered statistically significant. RESULTS: Immunohistochemical staining demonstrated that 138 of 214 gastric cancer samples (64.5%) were positive for galectin-1, and 116 out of 214 gastric cancer samples (54.2%) were positive for VEGF. There was a significant association between galectin-1 and VEGF expression; VEGF was detected in 60.1% of galectin-1-positive samples and 43.4% of galectin-1-negative samples (P < 0.05). Galectin-1 expression was associated with tumor size, tumor location, stage, lymph node metastases, and VEGF expression (all P < 0.05).

VEGF expression was related to tumor size, stage, and lymph node metastases (all  $P < 0.05$ ). The 5-year survival rate was 56.6% for galectin-1-positive patients and 69.2% for galectin-1-negative patients, and the prognosis for galectin-1-positive patients was significantly poorer compared with galectin-1-negative patients ( $\chi^2 = 13.880$ ,  $P = 0.000$ ). The 5-year survival rates for VEGF-positive and VEGF-negative patients were 53.4% and 70.5%, respectively ( $\chi^2 = 4.619$ ,  $P = 0.032$ ). The overall survival rate of patients with both galectin-1 and VEGF overexpression in gastric cancer tissue samples was significantly poorer than other groups (both  $P < 0.05$ ). **CONCLUSION:** Galectin-1 expression was positively associated with VEGF expression. Both galectin-1 and VEGF can serve as independent prognostic indicators of poor survival for gastric cancer after gastrectomy.

[431]

**TÍTULO / TITLE:** - Expression of Opa interacting protein 5 (OIP5) is associated with tumor stage and prognosis of clear cell renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Histochem. 2013 May 9. pii: S0065-1281(13)00059-7. doi: 10.1016/j.acthis.2013.03.008.

●●Enlace al texto completo (gratis o de pago)

[1016/j.acthis.2013.03.008](#)

**AUTORES / AUTHORS:** - Gong M; Xu Y; Dong W; Guo G; Ni W; Wang Y; Wang Y; An R

**INSTITUCIÓN / INSTITUTION:** - Department of Urological Surgery, The First Affiliated Hospital of Harbin Medical University, Harbin, China.

**RESUMEN / SUMMARY:** - Opa interacting protein 5 (OIP5), overexpressed in some types of human cancers, has been reported to be associated with the carcinogenesis of human cancer. However, the biological function and clinical significance of OIP5 in human Clear Cell Renal Cell Carcinoma (CCRCC) remains unknown. In the present study, we found the expression of OIP5 was markedly upregulated in surgical CCRCC specimens and CCRCC cell lines. Immunohistochemical analysis revealed that paraffin-embedded archival CCRCC specimens exhibited higher levels of OIP5 expression than normal renal tissues. Further statistical analysis suggested the upregulation of OIP5 was positively correlated with the Fuhrman grade ( $P=0.02$ ), T classification ( $P=0.015$ ), N classification ( $P=0.018$ ) and clinical stage ( $P=0.035$ ). Also, patients with high OIP5 expression dramatically exhibited shorter survival time ( $P=0.001$ ). In addition, the OIP5 expression was an independent prognostic marker of overall survival of CCRCC patients in a multivariate analysis ( $P=0.008$ ). Experimentally, we demonstrated that silencing OIP5 in CCRCC cell lines by specific siRNA clearly inhibited cell growth. In conclusion, our findings suggested that OIP5 could be a valuable marker of CCRCC progression and prognosis, and a promising therapeutic target for CCRCC.

[432]

**TÍTULO / TITLE:** - Usnic Acid inhibits growth and induces cell cycle arrest and apoptosis in human lung carcinoma A549 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65 Suppl 1:36-43. doi: 10.1080/01635581.2013.785007.

●●Enlace al texto completo (gratis o de pago)

[1080/01635581.2013.785007](#)

**AUTORES / AUTHORS:** - Singh N; Nambiar D; Kale RK; Singh RP

**INSTITUCIÓN / INSTITUTION:** - a School of Life Sciences, Central University of Gujarat, Gandhinagar, India.

**RESUMEN / SUMMARY:** - Usnic acid (UA) is a secondary metabolite abundantly found in lichens. Some studies have shown the anticancer potential of UA; however, its efficacy and associated mechanisms are yet to be fully explored. Herein, we assessed the anticancer potency and associated molecular alterations by UA in human lung carcinoma A549 cells. UA treatment (25-100  $\mu$ M) for 24 and 48 h decreased total cell number by 39-67% ( $P < 0.01$ ) and 68-89% ( $P < 0.001$ ), respectively, and enhanced cell death by up to twofold and eightfold ( $P < 0.001$ ), respectively. UA (1-10  $\mu$ M) also significantly ( $P < 0.001$ ) suppressed colony formation of A549 cells. The cell growth inhibition was associated with cell cycle arrest at G<sub>0</sub>/G<sub>1</sub> phase. UA decreased the expression of cyclin-dependent kinase (CDK)4, CDK6, and cyclin D1 and increased the expression of CDK inhibitor (CDKI) p21/cip1 protein. While examining the cell death associated molecular changes, we observed that UA induces mitochondrial membrane depolarization and led to more than twofold increase ( $P < 0.01$ ) in apoptotic cells. The apoptotic effect of UA was accompanied by enhanced poly(ADP-ribose) polymerase cleavage. This study shows that UA inhibits cell growth involving G<sub>0</sub>/G<sub>1</sub> phase cell cycle arrest and induces cell death via mitochondrial membrane depolarization and induction of apoptosis in human lung carcinoma cells.

[433]

**TÍTULO / TITLE:** - beta-Ionone Induces Cell Cycle Arrest and Apoptosis in Human Prostate Tumor Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65(4):600-10. doi: 10.1080/01635581.2013.776091.

●●Enlace al texto completo (gratis o de pago)

[1080/01635581.2013.776091](#)

**AUTORES / AUTHORS:** - Jones S; Fernandes NV; Yeganehjoo H; Katuru R; Qu H; Yu Z; Mo H

**INSTITUCIÓN / INSTITUTION:** - a Department of Nutrition and Food Sciences , Texas Woman's University , Denton , Texas , USA.

**RESUMEN / SUMMARY:** - 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase is the rate-limiting activity in the mevalonate pathway that provides essential intermediates for posttranslational modification of growth-associated proteins. Assorted dietary isoprenoids found in plant foods suppress HMG CoA reductase and have cancer chemopreventive activity. beta-Ionone, a cyclic sesquiterpene and an end-ring analog of beta-carotene, induced concentration-dependent inhibition of the proliferation of human DU145 (IC<sub>50</sub> = 210 μmol/L) and LNCaP (IC<sub>50</sub> = 130 μmol/L) prostate carcinoma cells and PC-3 prostate adenocarcinoma cells (IC<sub>50</sub> = 130 μmol/L). Concomitantly, beta-ionone-induced apoptosis and cell cycle arrest at the G1 phase in DU145 and PC-3 cells were shown by fluorescence microscopy, flow cytometry, and TUNEL reaction, and downregulation of cyclin-dependent kinase 4 (Cdk4) and cyclin D1 proteins. Growth suppression was accompanied by beta-ionone-induced downregulation of reductase protein. A blend of beta-ionone (150 μmol/L) and trans, trans-farnesol (25 μmol/L), an acyclic sesquiterpene that putatively initiates the degradation of reductase, suppressed the net growth of DU145 cells by 73%, an impact exceeding the sum of those of beta-ionone (36%) and farnesol (22%), suggesting a synergistic effect. beta-ionone, individually or in combination with other HMG CoA reductase suppressors, may have potential in prostate cancer chemoprevention and/or therapy.

[434]

**TÍTULO / TITLE:** - Differential Effect of Grape Seed Extract against Human Non-small-Cell Lung Cancer Cells: The Role of Reactive Oxygen Species and Apoptosis Induction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65 Suppl 1:44-53. doi: 10.1080/01635581.2013.785003.

●●Enlace al texto completo (gratis o de pago)

[1080/01635581.2013.785003](#)

**AUTORES / AUTHORS:** - Tyagi A; Raina K; Gangar S; Kaur M; Agarwal R; Agarwal C

**INSTITUCIÓN / INSTITUTION:** - a Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences , University of Colorado Anschutz Medical Campus , Aurora , Colorado , USA.

**RESUMEN / SUMMARY:** - The present study examines grape seed extract (GSE) efficacy against a series of non-small-cell lung cancer (NSCLC) cell lines that differ in their Kras and p53 status to establish GSE potential as a cytotoxic agent against a wide range of lung cancer cells. GSE suppressed growth and induced apoptotic death in NSCLC cells irrespective of their k-Ras status, with more sensitivity toward H460 and H322 (wt k-Ras) than A549 and H1299 cells

(mutated k-Ras). Mechanistic studies in A549 and H460 cells, selected, based on comparative efficacy of GSE at higher and lower doses, respectively, showed that apoptotic death involves cytochrome c release associated caspases 9 and 3 activation, and poly (ADP-ribose) polymerase cleavage, strong phosphorylation of ERK1/2 and JNK1/2, downregulation of cell survival proteins, and upregulated proapoptotic Bak expression. Importantly, GSE treatment caused a strong superoxide radical-associated oxidative stress, significantly decreased intracellular reduced glutathione levels, suggesting, for the first time, the involvement of GSE-caused oxidative stress in its apoptotic inducing activity in these cells. Because GSE is a widely-consumed dietary agent with no known untoward effects, our results support future studies to establish GSE efficacy and usefulness against NSCLC control.

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[435]

**TÍTULO / TITLE:** - Sanguinarine induces apoptosis in human colorectal cancer HCT-116 cells through ROS-mediated Egr-1 activation and mitochondrial dysfunction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Toxicol Lett. 2013 May 6;220(2):157-166. doi: 10.1016/j.toxlet.2013.04.020.

●●Enlace al texto completo (gratis o de pago)

[1016/j.toxlet.2013.04.020](#)

**AUTORES / AUTHORS:** - Han MH; Kim GY; Yoo YH; Choi YH

**INSTITUCIÓN / INSTITUTION:** - Department of Biomaterial Control (BK21 Program), Graduate School, Dongeui University, Busan 614-714, Republic of Korea.

**RESUMEN / SUMMARY:** - We examined the effects of sanguinarine, a benzophenanthridine alkaloid, on reactive oxygen species (ROS) production and the association of these effects with apoptotic cell death in a human colorectal cancer HCT-116 cell line. Sanguinarine generated ROS, which was followed by a decrease in the mitochondrial membrane potential (MMP), the activation of caspase-9 and -3, and the down-regulation of anti-apoptotic proteins, such as Bcl2, XIAP and cIAP-1. Sanguinarine also promoted the activation of caspase-8 and truncation of Bid (tBid). However, the quenching of ROS generation by N-acetyl-L-cysteine, a scavenger of ROS, reversed the sanguinarine-induced apoptosis effects via inhibition of the MMP collapse, tBid expression, and activation of caspases. Sanguinarine also markedly induced the expression of the early growth response gene-1 (Egr-1) during the early period, after which expression level was decreased. In addition, HCT-116 cells transfected with Egr-1 siRNA displayed significant blockage of sanguinarine-induced apoptotic activity in a ROS-dependent manner. These observations clearly indicate that ROS, which are key mediators of Egr-1 activation and MMP

collapse, are involved in the early molecular events in the sanguinarine-induced apoptotic pathway acting in HCT-116 cells.

[436]

**TÍTULO / TITLE:** - A potential rhodium cancer therapy: studies of a cytotoxic organorhodium(I) complex that binds DNA.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 May 1;23(9):2527-31. doi: 10.1016/j.bmcl.2013.03.016. Epub 2013 Mar 14.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.03.016](http://1016/j.bmcl.2013.03.016)

**AUTORES / AUTHORS:** - McConnell JR; Rananaware DP; Ramsey DM; Buys KN; Cole ML; McAlpine SR

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, University of New South Wales, Kensington, NSW 2052, Australia.

**RESUMEN / SUMMARY:** - Described is a novel organorhodium(I) complex that is cytotoxic to the colon cancer cell line HCT116 and alters cell migration, DNA replication, and DNA condensation. Most importantly, the mechanism observed is not seen for the parent organorhodium dimer complex  $[\{\text{RhCl}(\text{COD})\}_2]$ ,  $\text{RhCl}_3$ , or the free ligand/proligands (COD and 1-(n)butyl-3-methylimidazolium chloride). Thus, the activity of this organorhodium complex is attributable to its unique structure.

[437]

**TÍTULO / TITLE:** - Physalin A Induces Apoptotic Cell Death and Protective Autophagy in HT1080 Human Fibrosarcoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Nat Prod. 2013 May 24;76(5):880-8. doi: 10.1021/np400017k. Epub 2013 May 6.

●●Enlace al texto completo (gratis o de pago) [1021/np400017k](http://1021/np400017k)

**AUTORES / AUTHORS:** - He H; Zang LH; Feng YS; Wang J; Liu WW; Chen LX; Kang N; Tashiro S; Onodera S; Qiu F; Ikejima T

**INSTITUCIÓN / INSTITUTION:** - Department of Natural Products Chemistry, School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang, 110016, People's Republic of China.

**RESUMEN / SUMMARY:** - Physalin A (1) is a withanolide isolated from *Physalis alkekengi* var. *franchetii*. In this study, the selective growth inhibitory effects on tumor cells induced by 1 were screened, and the mechanism was investigated on 1-induced growth inhibition, including apoptosis and autophagy, in human fibrosarcoma HT1080 cells. Apoptosis induced by 1 in HT1080 cells was associated with up-regulation of caspase-3 and caspase-8 expression. However, there were no significant changes in caspase-9, Bid, Bax, and Bcl-2 expression, indicating that 1-induced apoptosis in HT1080 cells occurs mainly

through activation of the death receptor-associated extrinsic apoptotic pathways. Autophagy induced by 1 was found to antagonize apoptosis in HT1080 cells. This effect was enhanced by rapamycin and suppressed by the autophagy inhibitor 3-methyladenine (3MA). Loss of beclin 1 (as an autophagic regulator) function led to similar results to 3MA. However, 1 did not show inhibitory effects on normal human cells (human peripheral blood mononuclear cells). Taken together, these results suggest that 1 may be a promising agent for the treatment of cancer.

[438]

**TÍTULO / TITLE:** - Folate receptor alpha (FRA) expression remains unchanged in epithelial ovarian and endometrial cancer after chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Apr 2. pii: S0090-8258(13)00179-0. doi: 10.1016/j.ygyno.2013.03.024.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.03.024](#)

**AUTORES / AUTHORS:** - Despierre E; Lambrechts S; Leunen K; Berteloot P; Neven P; Amant F; O'Shannessy DJ; Somers EB; Vergote I

**INSTITUCIÓN / INSTITUTION:** - Gynecologic Oncology and Leuven Cancer Institute, University Hospitals Leuven, Department of Oncology, KU Leuven, Belgium. Electronic address: [evelyn.despierre@uzleuven.be](mailto:evelyn.despierre@uzleuven.be).

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Based on its expression profile, folate receptor alpha (FRA) is an attractive candidate for targeted diagnostics and therapeutics. However, applicability of these agents in residual or recurrent disease could be influenced by chemotherapy. We evaluated whether chemotherapy modified FRA expression in non-mucinous epithelial ovarian (EOC) and endometrial carcinoma (EC). **METHODS:** FRA staining was evaluated by immunohistochemistry, using MAb 26B3, in 81 patients (41 EOCs and 40 ECs) and 17 control tissues (5 benign ovarian cysts, 5 normal ovarian, and 7 normal endometrial tissues). Chemotherapy effect was evaluated in 42 patients (30 paired samples at primary and interval debulking surgery and 12 from primary and recurrent disease). FRA expression was assessed using a semi-quantitative staining algorithm, the M-score (range 0-50). **RESULTS:** Median difference in M-score between tumor and control samples was 27.5 for EOC (95% CI 10.0 to 45.0) and 6.7 for EC (95% CI -6.7 to 21.7). Paired samples from both primary and interval debulking surgery did not differ in FRA expression in EOC (median difference of M-score between paired samples of 0.0 [95% CI -2.6 to 2.6]). Recurrent EOC tumors reflected FRA status at diagnosis (median difference of M-score between paired samples of 3.3 [95% CI -7.0 to 13.6]). **CONCLUSIONS:** This study shows no significant difference in FRA expression after chemotherapy, strengthening the rationale for FRA

targeted diagnostics and therapeutics in FRA expressing tumors, whether newly diagnosed or at recurrence.

[439]

**TÍTULO / TITLE:** - Induction of apoptosis and antitumor effects of a small molecule inhibitor of Bcl-2 and Bcl-xl, gossypol acetate, in multiple myeloma in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 May 23. doi: 10.3892/or.2013.2489.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2489](#)

**AUTORES / AUTHORS:** - Lin J; Wu Y; Yang D; Zhao Y

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatric Hematology, Chinese PLA General Hospital, Beijing 100853, P.R. China.

**RESUMEN / SUMMARY:** - Gossypol is a naturally occurring polyphenolic compound extracted from cotton plants. Recent studies revealed that gossypol is a non-peptidic small molecule inhibitor of Bcl-2/Bcl-xl. The aim of the present study was to investigate the induction of apoptosis and antitumor effects of gossypol acetate in multiple myeloma and the possible mechanism(s) of action. Our results showed that gossypol acetate resulted in a dose- and time-dependent inhibition of multiple myeloma cell proliferation, with an IC50 value to both U266 and Wus1 cells at 2.4, 2.2 microM at 48 h after treatment. Gossypol acetate effectively induced the apoptosis of multiple myeloma cells as demonstrated by typical morphological changes, DNA ladder formation and increase in the percentage of cells in subdiploid peak. Furthermore, colorimetric assays showed activation of both caspase-3 and caspase-9. Bcl-2 and Bcl-xl expression was decreased by 86.5+/-1.2% and 35.9+/-3.6%, respectively, after treatment with gossypol acetate at 25 micromol/l for 24 h. Preliminary studies in vivo showed that a growth inhibition (T/C) of 30.9% (gossypol acetate 40 mg/kg) was obtained in Balb/C mice bearing Wus1 cells. In addition, there was no body weight loss for the treated group in comparison with the vehicle mice. Our results demonstrated that the potent inhibitor of Bcl-2 and Bcl-xl gossypol acetate had significant antiproliferative and antiapoptotic effects on multiple myeloma cells in vitro and in vivo. Gossypol acetate may represent a promising new anticancer agent with a novel molecular mechanism and warrants further investigation as a single agent, or in combination with other chemotherapeutics, for human multiple myeloma with Bcl-2 overexpression.

[440]

**TÍTULO / TITLE:** - Effect of caffeic acid on Ca homeostasis and apoptosis in SCM1 human gastric cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Toxicol. 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s00204-013-1075-](http://1007/s00204-013-1075-8)

[8](#)

**AUTORES / AUTHORS:** - Chang HT; Chen IL; Chou CT; Liang WZ; Kuo DH; Shieh P; Jan CR

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, 813, Taiwan.

**RESUMEN / SUMMARY:** - Caffeic acid is a natural phenolic compound that affects cellular Ca<sup>2+</sup> homeostasis and viability in different cells. This study examined the effect of caffeic acid on cytosolic free Ca<sup>2+</sup> concentrations ([Ca<sup>2+</sup>]<sub>i</sub>) and viability in SCM1 human gastric cancer cells. The Ca<sup>2+</sup>-sensitive fluorescent dye fura-2 was used to measure [Ca<sup>2+</sup>]<sub>i</sub>. Caffeic acid-evoked [Ca<sup>2+</sup>]<sub>i</sub> rises concentration dependently. The response was reduced by removing extracellular Ca<sup>2+</sup>. Caffeic acid-evoked Ca<sup>2+</sup> entry was inhibited by store-operated channel inhibitors (nifedipine, econazole, and SK&F96365) and protein kinase C activator (phorbol 12-myristate 13 acetate, PMA), but not by protein kinase C inhibitor (GF109203X). In Ca<sup>2+</sup>-free medium, treatment with the endoplasmic reticulum Ca<sup>2+</sup> pump inhibitor thapsigargin or 2,5-di-tert-butylhydroquinone (BHQ) abolished caffeic acid-evoked [Ca<sup>2+</sup>]<sub>i</sub> rise. Conversely, treatment with caffeic acid decreased thapsigargin or BHQ-evoked [Ca<sup>2+</sup>]<sub>i</sub> rise. Inhibition of phospholipase C with U73122 abolished caffeic acid-evoked [Ca<sup>2+</sup>]<sub>i</sub> rise. At 200-800 μM, caffeic acid inhibited cell viability, which was not changed by chelating cytosolic Ca<sup>2+</sup> with 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid-acetoxymethyl ester (BAPTA/AM). Caffeic acid between 400 and 800 μM also induced apoptosis. Collectively, in SCM1 cells, caffeic acid-induced [Ca<sup>2+</sup>]<sub>i</sub> rises by evoking phospholipase C-dependent Ca<sup>2+</sup> release from the endoplasmic reticulum and Ca<sup>2+</sup> entry via store-operated Ca<sup>2+</sup> channels. Caffeic acid also caused Ca<sup>2+</sup>-independent apoptosis.

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[441]

**TÍTULO / TITLE:** - ER stress and ASK1-JNK activation contribute to oridonin-induced apoptosis and growth inhibition in cultured human hepatoblastoma HuH-6 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cell Biochem. 2013 Jul;379(1-2):161-9. doi: 10.1007/s11010-013-1638-2. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1007/s11010-013-1638-](http://1007/s11010-013-1638-2)

[2](#)

**AUTORES / AUTHORS:** - Cai DT; Jin H; Xiong QX; Liu WG; Gao ZG; Gu GX; Qiu YH

**INSTITUCIÓN / INSTITUTION:** - The seven ward, Department of Surgery, The Children's Hospital affiliated to Medical School of Zhejiang University, 57 Zu-

gan Lane, Xia-cheng District, Hangzhou, 310000, Zhejiang, China,  
[duotecai@yahoo.com](mailto:duotecai@yahoo.com).

**RESUMEN / SUMMARY:** - Oridonin, the main active component of *Rabdosia rubescens*, has antitumor activities in experimental and clinical settings. The aims of the current study were to explore the anticancer abilities of oridonin in hepatoblastoma (HB) HuH-6 cells and to investigate the underlying mechanisms. We found that oridonin inhibited HuH-6 cell in vitro growth in a dose- and time-dependent manner. Further, oridonin induced HuH-6 cell apoptosis and G2/M cell cycle arrest. Upon studying the mechanism, we found that oridonin treatment caused endoplasmic reticulum (ER) stress activation. Meanwhile, ER stress inhibitor salubrinal- or inositol-requiring enzyme 1 (IRE-1) shRNA silencing inhibited oridonin's anti-HuH-6 effects, while ER stress inducers thapsigargin (Tg) and tunicamycin™ mimicked oridonin's actions on HuH-6 cells. Oridonin also activated apoptosis signal regulating kinase 1 (ASK1)-c-Jun N-terminal kinase 1 (JNK1) signaling in cultured HuH-6 cells, which was inhibited by IRE-1 silencing. Importantly, the JNK inhibitors suppressed oridonin-induced growth inhibition and apoptosis in HuH-6 cells. In conclusion, our results suggest that oridonin induces growth inhibition and apoptosis in cultured HuH-6 cells involving ER stress and ASK1/JNK signaling pathways, which enhances our understanding of the molecular mechanisms of oridonin in HB management.

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[442]

**TÍTULO / TITLE:** - Interferons as inducers of apoptosis in malignant cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Interferon Cytokine Res. 2013 Apr;33(4):162-70. doi: 10.1089/jir.2012.0110.

●●Enlace al texto completo (gratis o de pago) [1089/jir.2012.0110](http://1089/jir.2012.0110)

**AUTORES / AUTHORS:** - Kotredes KP; Gamero AM

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Temple University School of Medicine, Philadelphia, PA 19140, USA.

**RESUMEN / SUMMARY:** - Discovered as antiviral cytokines, interferons (IFNs) are now also recognized for their capacity to inhibit the growth of malignant cells via activation of programmed cell death, better known as apoptosis. In this review, we will cover recent advances made in this field, as it pertains to the various proposed mechanisms of IFN-induced apoptosis and the characterization of IFN-responsive genes not previously known to have apoptotic function. Also mentioned here is a description of the activation and crosstalk of survival signaling pathways as a mode of IFN resistance that remains a persistent clinical adversary to overcome and the future of IFNs as antitumor agents.

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[443]

**TÍTULO / TITLE:** - Impaired Gating of an L-Type Ca(2+) Channel Carrying a Mutation Linked to Malignant Hyperthermia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biophys J. 2013 May 7;104(9):1917-22. doi: 10.1016/j.bpj.2013.03.035.

●●Enlace al texto completo (gratis o de pago) [1016/j.bpj.2013.03.035](#)

**AUTORES / AUTHORS:** - Bannister RA; Beam KG

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Cardiology Division, University of Colorado Denver-Anschutz Medical Campus, Aurora, Colorado. Electronic address: [roger.bannister@ucdenver.edu](mailto:roger.bannister@ucdenver.edu).

**RESUMEN / SUMMARY:** - Recently, we characterized the functional properties of a mutant skeletal muscle L-type Ca(2+) channel (CaV1.1 R174W) linked to the pharmacogenetic disorder malignant hyperthermia. Although the R174W mutation neutralizes the innermost basic amino acid in the voltage-sensing S4 helix of the first conserved membrane repeat of CaV1.1, the ability of the mutant channel to engage excitation-contraction coupling was largely unaffected by the introduction of the bulky tryptophan residue. In stark contrast, the mutation ablated the ability of CaV1.1 to produce L-type current under our standard recording conditions. In this study, we have investigated the mechanism of channel dysfunction more extensively. We found that CaV1.1 R174W will open and conduct Ca(2+) in response to strong or prolonged depolarizations in the presence of the 1,4-dihydropyridine receptor agonist +/- Bay K 8644. From these results, we have concluded that the R174W mutation impedes entry into both mode 1 (low Po) and mode 2 (high Po) gating states and that these gating impairments can be partially overcome by maneuvers that promote entry into mode 2.

[444]

**TÍTULO / TITLE:** - Melatonin attenuates dexamethasone toxicity-induced oxidative stress, calpain and caspase activation in human neuroblastoma SH-SY5Y cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Steroid Biochem Mol Biol. 2013 May 17. pii: S0960-0760(13)00072-1. doi: 10.1016/j.jsbmb.2013.04.008.

●●Enlace al texto completo (gratis o de pago)

[1016/j.jsbmb.2013.04.008](#)

**AUTORES / AUTHORS:** - Suwanjang W; Abramov AY; Govitrapong P; Chetsawang B

**INSTITUCIÓN / INSTITUTION:** - Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Nakhonpathom, Thailand.

**RESUMEN / SUMMARY:** - Glucocorticoids (GCs) have a significant role in the adaptive response of the brain to stress. Increasing evidence has demonstrated that an increase of GC levels may induce neuronal cell death via apoptotic

pathways. There is a correlation between over-production of reactive oxygen species (ROS) and an elevation in cytosolic calcium that causes a subsequent increase in the calcium-dependent death-process activation in GC-induced toxicity. Consequently, melatonin, via its antioxidant activity, exhibits a neuroprotective effect against apoptosis induced by intracellular calcium overload. Therefore, in the present study, we explored the protective effect of melatonin in GC-induced toxicity in dopaminergic SH-SY5Y cells. Cellular treatment with the synthetic GCs, dexamethasone (DEX), resulted in a marked decrease in cell viability and in the level of the calpain-inhibitor protein, calpastatin. DEX-induced toxicity also caused an increase in ROS production and the activation of the calcium-dependent cysteine protease, calpain, along with an increase in caspase-3 activation. Pretreatment of the cells with melatonin substantially prevented the decrease in cell viability, over-production of ROS and the activation of calpain and caspase-3, and reversed the depletion in calpastatin levels. These results suggest that melatonin may exert its protective effects against the calpain- and caspase-dependent death process in DEX-induced neurotoxicity.

[445]

**TÍTULO / TITLE:** - Prognosis of core-binding factor acute myeloid leukemia after first relapse.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 May 28.

●●Enlace al texto completo (gratis o de pago)

[3324/haematol.2012.078030](#)

**AUTORES / AUTHORS:** - Kurosawa S; Miyawaki S; Yamaguchi T; Kanamori H; Sakura T; Moriuchi Y; Sano F; Kobayashi T; Yasumoto A; Hatanaka K; Yanada M; Nawa Y; Takeuchi J; Nakamura Y; Fujisawa S; Shibayama H; Miura I; Fukuda T

**INSTITUCIÓN / INSTITUTION:** - National Cancer Center Hospital;

**RESUMEN / SUMMARY:** - Abstract Core binding factor acute myeloid leukemia is known to have a favorable prognosis, however, there have been no detailed analyses on prognostic factors after first relapse. Using a nation-wide database, we retrospectively analyzed core binding factor acute myeloid leukemia patients who relapsed after being treated with chemotherapy alone during their first complete remission. Of a total of 397 patients who were diagnosed with core binding factor acute myeloid leukemia, 208 experienced a first relapse, and analyses were performed in 139 patients for whom additional data were available. In the entire cohort, overall survival after relapse was 48% at 3 years. By a multivariate analysis, a younger age at diagnosis, the longer interval to relapse, and inv(16) were shown to be independently associated with better survival after relapse. Although there was no significant difference in survival after relapse between patients who received allogeneic hematopoietic cell

transplantation and those who did not in the overall relapsed patients, we found that transplantation significantly improved survival among patients who had t(8;21) (54% vs 26% at 3 years, p=0.002). In addition, among patients with t(8;21), those who had different cytogenetics at relapse had a significantly improved survival after transplantation, however, those who had same cytogenetics did not. We showed that the prognosis significantly differs and optimal treatment strategies may vary between groups of core binding factor acute myeloid leukemia patients with different cytogenetic profiles at relapse. These findings may help to guide therapeutic decisions after first relapse.

[446]

**TÍTULO / TITLE:** - Squamous cell carcinoma antigen: A potentially useful prognostic marker in squamous cell carcinoma of the anal canal and margin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer. 2013 Apr 10. doi: 10.1002/cncr.28055.

●●Enlace al texto completo (gratis o de pago) [1002/cncr.28055](#)

**AUTORES / AUTHORS:** - Williams M; Swampillai A; Osborne M; Mawdsley S; Hughes R; Harrison M; Harvey R; Glynn-Jones R

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, University College Hospital, London, United Kingdom.

**RESUMEN / SUMMARY:** - BACKGROUND: The objective of this retrospective study was to investigate the predictive value of pretreatment serum squamous cell carcinoma antigen (SCCAg) levels in 174 patients with squamous cell carcinoma of the anus who received concurrent chemoradiation between 1997 and 2010. METHODS: Pretreatment serum SCCAg measurements in patients with histologically diagnosed squamous cell carcinoma of the anal canal and margin who received chemoradiation were compared with clinical tumor classification and lymph node status for prognostic/predictive ability, including 1) tumor response after the completion of chemoradiation treatment, 2) disease recurrence, and 3) overall survival. Clinical measurements and scores were compared using Spearman rank tests, and survival was assessed in both univariate and multivariate survival analyses. RESULTS: The median pretreatment levels of SCCAg according to clinical tumor classification and clinical lymph node status were 0.8 mug/L in T1 tumors, 1.90 mug/L in T2 tumors, 2.5 mug/L in T3 tumors, 3.8 mug/L in T4 tumors, 1.35 mug/L in patients with N0 status, and 3.05 mug/L in patients with N0+ status (correlation coefficient: T-classification, 0.43; lymph node status, 0.38; both P < .00001). Of the patients who had normal SCCAg levels, 95% achieved a complete response after initial treatment; and, of those who had elevated SCCAg levels, 86% achieved a complete response (P = .05). Overall survival (hazard ratio, 2.5; P = .007) and disease-free survival (hazard ratio, 2.2; P = .058) were worse for those who had elevated pretreatment serum SCCAg concentrations. CONCLUSIONS: Pretreatment SCCAg levels in patients with squamous cell

carcinoma of the anal canal and margin were correlated with clinical tumor classification and clinical lymph node status. Elevated levels of SCCAg were associated with a reduced chance of achieving a complete response and an increased chance of recurrence and death. The authors recommend further studies to determine the prognostic value of SCCAg in anal squamous cell carcinoma and suggest the potential use of SCCAg as a stratification factor in future trials. Cancer 2013;000:000-000. © 2013 American Cancer Society.

[447]

**TÍTULO / TITLE:** - Tandem therapy for retinoblastoma: immunotherapy and chemotherapy enhance cytotoxicity on retinoblastoma by increasing apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s00432-013-1448-](#)

[7](#)

**AUTORES / AUTHORS:** - Liu Q; Wang Y; Wang H; Liu Y; Liu T; Kunda PE

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, The General Hospital of the Chinese People's Armed Police Forces, Beijing, 100039, China.

**RESUMEN / SUMMARY:** - PURPOSE: The goal of this study was to provide an experimental basis for the clinical application of cell immunotherapy on RB in combination with chemotherapy treatment and to explore the mechanism of their combined cytotoxicity. METHODS: We investigated the antitumor effect of cytokine-induced killer cells (CIK), co-cultivated with dendritic cells pulsed with tumor antigens (DC-Ag) and/or with carboplatin. Cytotoxicity was evaluated on a retinoblastoma cell line (RB-Y79) by FCM and immunofluorescence microscopy. Time-lapse video microscopy was used to follow the sequence of events during the carboplatin and CIK cytotoxicity. RESULTS: Our results showed that a small proportion of RB-Y79 cells died after a low-dose carboplatin application. The cell population recovered 5 days after carboplatin was removed from the culture medium. Three times fewer normal epithelium retina cell lines (hTERT-RPE1) died at the same carboplatin dose. CIK achieved 5 times more cytotoxicity against RB cells pre-treated with low dose of carboplatin, showing the highest antitumor activity in the tandem carboplatin-DC-Ag-CIK-carboplatin treatment. Time-lapse video microscopy revealed that carboplatin-preconditioned RB cells are more avidly engaged by CIK cells, increasing RB mortality and resulting in an overall increment in apoptosis. CONCLUSION: This study provides evidence that carboplatin combined with cell immunotherapy is superior to carboplatin alone to kill RB cells in vitro. We propose that a primary application of a low dose of a chemotherapeutic drug that is able to attack the tumor, and a subsequent treatment with highly effective immunotherapy based on DC-Ag-CIK cells could be a safe and selective treatment for RB.

[448]

**TÍTULO / TITLE:** - The influence of cylindrospermopsin on oxidative DNA damage and apoptosis induction in HepG2 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chemosphere. 2013 Jun;92(1):24-30. doi: 10.1016/j.chemosphere.2013.03.023. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago)

[1016/j.chemosphere.2013.03.023](http://1016/j.chemosphere.2013.03.023)

**AUTORES / AUTHORS:** - Straser A; Filipic M; Gorenc I; Zegura B

**INSTITUCIÓN / INSTITUTION:** - National Institute of Biology, Department of Genetic Toxicology and Cancer Biology, Vecna pot 111, 1000 Ljubljana, Slovenia. Electronic address: [alja.straser@nib.si](mailto:alja.straser@nib.si).

**RESUMEN / SUMMARY:** - Cylindrospermopsin (CYN) a potent cyanobacterial cytotoxin and protein synthesis inhibitor is increasingly being found in surface freshwaters worldwide. Due to its genotoxic activity and potential carcinogenicity it was recognized as a potential threat to humans. However, the mechanisms of CYN genotoxicity are not well understood. We explored whether CYN at non-cytotoxic exposure conditions causes DNA damage through induction of oxidative stress and whether it induces apoptosis in HepG2 cells. With the DCFH-DA probe a significant increase in the intracellular formation of reactive oxygen species (ROS) was observed, which steadily increased with incubation. Induction of oxidative DNA damage was determined with the modified comet assay with formamidopyrimidine glycosylase (Fpg) digestion. No DNA damage was observed after 4h exposure to CYN. After 12 and 24h exposure, CYN (at 0.25 and 0.5µg/mL(-1)) induced significant increase of DNA strand breaks, but not oxidative DNA damage, suggesting minor role of oxidative stress in CYN mediated genotoxicity. CYN also significantly increased the mitochondrial membrane potential (MMP), determined with the JC-1 probe, while no induction of caspase 3 and 7 activity and no increase in the number of apoptotic cells, measured with Annexin V/PI staining, could be determined. These results show that at non-cytotoxic concentrations CYN induced DNA damage was not the consequence of oxidative stress and that CYN did not induce apoptosis, which may add to the hazard of this toxin, as cells with damaged DNA are not removed from the population, enhancing the risk of mutations and consequently carcinogenesis.

[449]

**TÍTULO / TITLE:** - The Response to Second-line Induction with Bortezomib and Dexamethasone is Predictive of Long-term Outcomes Prior to High-dose Chemotherapy with Autologous Stem Cell Transplantation for Multiple Myeloma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Intern Med. 2013;52(9):961-8. Epub 2012 Mar 1.

**AUTORES / AUTHORS:** - Kobayashi T; Kuroda J; Fuchida S; Murakami S; Hatsuse M; Okano A; Iwai T; Tsutsumi Y; Kamitsuji Y; Akaogi T; Kawata-Iida E; Shimizu D; Uchiyama H; Matsumoto Y; Horiike S; Nakao M; Takahashi R; Kaneko H; Uoshima N; Kobayashi Y; Shimazaki C; Taniwaki M

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Japan.

**RESUMEN / SUMMARY:** - Objective We retrospectively investigated the efficacy and predictive factors for the treatment outcomes of bortezomib plus dexamethasone (BD) as second-line induction therapy prior to high-dose chemotherapy supported by autologous stem cell transplantation (HDT/ASCT) in multiple myeloma (MM) patients. Methods Sixty-six transplant eligible MM patients treated by the Kyoto Clinical Hematology Study Group between 2006 and 2011 were investigated. Conventional induction chemotherapy, including vincristine, doxorubicin and dexamethasone (VAD) and high-dose dexamethasone (HDD), was used as first-line induction therapy in all patients, seven (10.6%) of whom attained a very good partial response (VGPR). Of the 59 patients who did not attain VGPR with VAD or HDD, 33 were given BD as second-line induction therapy prior to HDT/ASCT. Results Patients not treated with BD induction showed an overall response rate (ORR, i.e., better than partial response) of 85.3% after induction therapy, while the ORR of patients treated with BD induction improved from 42.4% after conventional induction therapy to 84.8% after BD. The overall survival (OS) and progression-free survival (PFS) of patients not treated with BD induction were not significantly influenced by the response to induction therapy. Among the patients treated with BD, failure in attaining VGPR prior to ASCT was associated with a significantly shorter PFS and it also tended to show a shorter OS, while the disease stage and achievement of a complete response after HDT/ASCT had no impact on OS or PFS. Conclusion The achievement of at least VGPR with second-line BD induction therapy is a prerequisite for attaining longer OS and PFS after HDT/ASCT.

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[450]

**TÍTULO / TITLE:** - Caudatin induces cell apoptosis in gastric cancer cells through modulation of Wnt/beta-catenin signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 May 27. doi: 10.3892/or.2013.2495.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2495](#)

**AUTORES / AUTHORS:** - Li X; Zhang X; Liu X; Tan Z; Yang C; Ding X; Hu X; Zhou J; Xiang S; Zhou C; Zhang J

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Protein Chemistry and Developmental Biology of the State Education Ministry of China, College of Life Science, Hunan Normal University, Changsha, Hunan 410081, P.R. China.

**RESUMEN / SUMMARY:** - Caudatin has been reported to trigger apoptosis in several types of cancer cell lines. In the present study, we investigated whether caudatin has therapeutic value in gastric cancer and examined the effects of caudatin on the expression of beta-catenin in human gastric carcinoma cell lines. Here, we showed that caudatin treatment resulted in a dose- and time-dependent inhibition of proliferation of the gastric carcinoma cell lines. Cell cycle analysis demonstrated that caudatin induced G0/G1 arrest and downregulated CDK2 levels. In contrast, the expression of the p21 protein was increased. AGS cells treated with caudatin exhibited typical characteristics of apoptosis, which were accompanied by activation of caspase3, 8, 9 and PARP. Western blot analysis and immunocytochemical staining showed that caudatin induced a reduction in betacatenin expression and this reduction was due to proteasome-mediated degradation. This reduction in betacatenin activation was due to the downregulation of its downstream targets cyclinD1 and cMYC in all gastric carcinoma cell lines. Furthermore, we demonstrated that gastric adenocarcinoma tissues and AGS cells exhibited abnormal expression of miR372. Additionally, caudatin downregulated the expression of oncomir miR372 and miR21, and upregulated tumor suppressor let7a miRNA expression. These data revealed that inhibition of Wnt/betacatenin signaling is a novel mechanism of action for caudatin during therapeutic intervention in gastric cancers.

[451]

**TÍTULO / TITLE:** - Alantolactone induces apoptosis in chronic myelogenous leukemia sensitive or resistant to imatinib through NF-kappaB inhibition and Bcr/Abl protein deletion.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Apoptosis. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [1007/s10495-013-0854-](#)

[2](#)

**AUTORES / AUTHORS:** - Wei W; Huang H; Zhao S; Liu W; Liu CX; Chen L; Li JM; Wu YL; Yan H

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Rui-Jin Hospital, Shanghai Jiao-Tong University School of Medicine, No. 197, Ruijin Er Road, Shanghai, 200025, China.

**RESUMEN / SUMMARY:** - Alantolactone, an allergenic sesquiterpene lactone, has recently been found to have significant antitumor effects on malignant tumor cells. Here, we investigated the potential effect of alantolactone on Bcr/Abl+ imatinib-sensitive and -resistant cells. Alantolactone treatment resulted in obvious apoptosis in both imatinib-sensitive and -resistant K562 cells, as shown by the increase in Annexin V-positive cells, caspase-3 activation, poly(ADP-ribose) polymerase-1 (PARP-1) cleavage and mitochondrial membrane potential collapse. Alantolactone significantly inhibited NF-kappaB-dependent

reporter gene activity, decreased the DNA-binding activity of NF- $\kappa$ B, and blocked TNF- $\alpha$ -induced I $\kappa$ B phosphorylation. Of interest, the oncogenic Bcr/Abl fusion protein but not its mRNA levels were quickly reduced upon alantolactone exposure in imatinib-sensitive and -resistant K562 cells. Bcr/Abl knockdown enhanced the apoptosis driven by alantolactone. Bcr/Abl protein reduction could not be reversed by the addition of proteasome or caspase-3 inhibitors. The overexpression of p65 inhibited alantolactone-induced apoptosis, whereas p65 or Bcr/Abl silencing enhanced its apoptotic-inducing effect. Furthermore, Bcr/Abl-transfected 32D cells showed more sensitivity to alantolactone than vector-transfected control cells, and the Bcr/Abl protein was depleted, as observed in K562 cells. Finally, alantolactone-induced apoptosis was also observed in primary CD34+ CML leukemic cells. Collectively, these findings suggest that alantolactone is a promising potent agent to fight against CML cells via the inhibition of the NF- $\kappa$ B signaling pathway and depletion of the Bcr/Abl protein.

[452]

**TÍTULO / TITLE:** - Raf kinase inhibitor protein inhibits esophageal cancer cell invasion through downregulation of matrix metalloproteinase expression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):304-12. doi: 10.3892/or.2013.2464. Epub 2013 May 14.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2464](#)

**AUTORES / AUTHORS:** - Zhao D; Ma J; Shi J; Cheng L; Li F; Jiang X; Jiang H

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, The Second Hospital of Hebei Medical University, Hebei Key Laboratory of Gastroenterology, Hebei Institute of Gastroenterology, Shijiazhuang, Hebei 050000, P.R. China.

**RESUMEN / SUMMARY:** - Esophageal cancer is the eighth most common malignant tumor in the world and is a common cause of tumor-related death. The development of esophageal cancer is a complex process involving many pathogenetic factors, multiple stages and accumulation of multiple gene mutations and interactions. This study aimed to investigate the effects of Raf kinase inhibitor protein (RKIP) on the proliferation, apoptosis and invasion of TE-1 esophageal cancer cells. Surgical specimens from esophageal cancer patients were classified into esophageal cancer tissues, tumor-adjacent tissues and normal esophageal tissues. The tissues were fixed in 4% paraformaldehyde solution for hematoxylin and eosin and immunohistochemical staining. RKIP expression in esophageal tissues was detected by immunohistochemical staining. The esophageal cancer cell line TE-1 was exposed to four different viruses: RKIP-RNAi-AD, NC-RNAi-GFP-AD, RKIP-AD and GFP-AD. Cell proliferation was detected by MTT assay and cell apoptosis was detected by flow cytometry. Cell invasion was determined by a Transwell

coated with Matrigel. RKIP, phospho-RKIP, Raf-1, phospho-Raf-1, ERK1/2, phospho-ERK1/2, GRK-2 and GAPDH expression was assayed by western blotting. LIN28 and MMP-14 mRNA was assayed by qPCR. The results showed that RKIP expression was reduced in esophageal cancer tissues in comparison with expression in normal esophageal epithelium tissues and tumor-adjacent tissues. Reduced RKIP expression was associated with lymph node or distant metastasis in esophageal cancer. RKIP inhibited the invasive and metastatic abilities of esophageal cancer cell line TE-1 by downregulating mRNA expression of LIN28 and MMP-14. RKIP had no effect on the MAPK signaling pathway in the esophageal cancer cell line TE-1, but was involved in the G protein-coupled signaling pathway. Our findings clearly demonstrate that RKIP inhibits esophageal cancer cell invasion by downregulating the expression of GRK-2, LIN28 and MMP-14.

[453]

**TÍTULO / TITLE:** - The in vitro antitumor activity of *Siegesbeckia glabrescens* against ovarian cancer through suppression of receptor tyrosine kinase expression and the signaling pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):221-6. doi: 10.3892/or.2013.2468. Epub 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2468](#)

**AUTORES / AUTHORS:** - Cho YR; Choi SW; Seo DW

**INSTITUCIÓN / INSTITUTION:** - College of Pharmacy, Dankook University, Cheonan 330-714, Republic of Korea.

**RESUMEN / SUMMARY:** - *Siegesbeckia glabrescens* (SG) Makino (Compositae) has been used as a traditional medicine for the treatment of a variety of diseases such as allergy, inflammation, acute hepatitis and hypertension. The primary aim of this study was to determine whether the ethanol extract of SG has antitumor activity against ovarian cancer and to identify molecular mechanisms and targets involved in the regulation of cell growth and progression. We demonstrate that SG treatment inhibits proliferation, adhesion, migration and invasion of SKOV-3 human ovarian cancer cells. The anti-proliferative effect of SG on SKOV-3 cells is accompanied by reduced expression of cyclin E and enhanced expression of the cyclin-dependent kinase inhibitor p27Kip1, leading to inhibition of pRb phosphorylation. We also show that these antitumor activities are found to be mediated through suppression of FAK, ERK, Akt and p70S6K-dependent signaling pathways and downregulation of receptor tyrosine kinases such as EGFR, VEGFR-2 and FGFR-1 as well as the cell adhesion molecule N-cadherin. Taken together, our findings suggest further development and evaluation of SG for the treatment of ovarian cancer.

[454]

**TÍTULO / TITLE:** - Verrucarín A, a protein synthesis inhibitor, induces growth inhibition and apoptosis in breast cancer cell lines MDA-MB-231 and T47D.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biotechnol Lett. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s10529-013-1238-](#)

[y](#)

**AUTORES / AUTHORS:** - Palanivel K; Kanimozhi V; Kadalmani B; Akbarsha MA

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**RESUMEN / SUMMARY:** - Verrucarín A (VA), a protein synthesis inhibitor, derived from the pathogen fungus *Myrothecium verrucaria*, inhibits growth of leukemia cell lines and activates caspases and apoptosis and inflammatory signaling in macrophages. We have investigated VA-induced growth inhibition in breast cancer cells MDA-MB-231 and T47D and, particularly, the mechanism of VA-induced apoptosis. VA treatment brought about apoptotic cell death in a dose- and time-dependent manner which was associated with chromatin condensation, cell shrinkage, nuclear fragmentation and intracellular ROS production. Mitochondrial membrane depolarization, activation of caspase-3, down-regulation of Bcl-2 expression and up-regulation of Bax and p53 expression were observed. VA thus affects the viability of both the breast cancer cells by triggering ROS-mediated intrinsic mechanism of apoptosis.

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[455]

**TÍTULO / TITLE:** - Class III beta-tubulin overexpression in ovarian clear cell and serous carcinoma as a marker for poor overall survival after platinum/taxane chemotherapy and sensitivity to paclitaxel.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Obstet Gynecol. 2013 Apr 10. pii: S0002-9378(13)00373-6. doi: 10.1016/j.ajog.2013.04.017.

●●Enlace al texto completo (gratis o de pago) [1016/j.ajog.2013.04.017](#)

**AUTORES / AUTHORS:** - Roque DM; Bellone S; Buza N; Romani C; Cocco E; Bignotti E; Ravaggi A; Rutherford TJ; Schwartz PE; Pecorelli S; Santin AD

**INSTITUCIÓN / INSTITUTION:** - Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT.

**RESUMEN / SUMMARY:** - OBJECTIVE: Clear cell carcinoma of the ovary is a distinct subtype of epithelial cancer associated with chemoresistance and poor outcome compared with serous papillary carcinomas. Resistance to paclitaxel has been linked to serous papillary overexpression of class III beta-tubulin in several human cancers but inadequately characterized among clear cell carcinoma of the ovary. Chemoresistance has also been variably linked to the

drug efflux pump p-glycoprotein. Epothilones are microtubule-stabilizing agents with putative activity in paclitaxel-resistant malignancies. In this study, we clarify the relationship between class III beta-tubulin and p-glycoprotein expression in clear cell carcinoma of the ovary, clinical outcome, and in vitro responsiveness to patupilone and paclitaxel. **STUDY DESIGN:** Class III beta-tubulin and p-glycoprotein were quantified by real time polymerase chain reaction in 61 fresh-frozen tissue samples and 11 cell lines. Expression by polymerase chain reaction was correlated with immunohistochemistry and overall survival. IC50 was determined using viability/metabolic assays. Impact of class III beta-tubulin down-regulation on IC50 was assessed with small interfering RNAs. **RESULTS:** Clear cell carcinoma of the ovary overexpressed class III beta-tubulin and p-glycoprotein relative to serous papillary carcinomas carcinomas in fresh-frozen tissues and cell lines. Class III beta-tubulin immunohistochemistry reflected real time polymerase chain reaction results and overexpression stratified patients by overall survival. P-glycoprotein correlated with in vitro paclitaxel resistance, but not clinical outcome. Clear cell carcinoma of the ovary were exquisitely sensitive to patupilone in a manner that correlated with class III beta-tubulin expression. **CONCLUSION:** Class III beta-tubulin overexpression in clear cell carcinoma of the ovary discriminates poor prognosis, serves as a marker for sensitivity to patupilone, and may contribute to paclitaxel resistance. Immunohistochemistry reliably identifies tumors with overexpression of class III beta-tubulin, and accordingly a subset of individuals likely to respond to patupilone.

[456]

**TÍTULO / TITLE:** - Ruthenium (II) polypyridyl complexes stabilize the bcl-2 promoter quadruplex and induce apoptosis of Hela tumor cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biometals. 2013 Mar 30.

●●Enlace al texto completo (gratis o de pago) [1007/s10534-013-9622-](#)

[6](#)

**AUTORES / AUTHORS:** - Wang C; Yu Q; Yang L; Liu Y; Sun D; Huang Y; Zhou Y; Zhang Q; Liu J

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, Jinan University, Guangzhou, 510632, People's Republic of China.

**RESUMEN / SUMMARY:** - In the present study, the interaction between GC-rich sequence of bcl-2 gene P1 promoter (Pu39) and two ruthenium (II) polypyridyl complexes, [Ru(bpy)<sub>2</sub>(tip)]<sup>2+</sup> (1) and [Ru(phen)<sub>2</sub>(tip)]<sup>2+</sup> (2), was investigated by UV-Visible, fluorescence spectroscopy, circular dichroism, fluorescence resonance energy transfer melting assay and polymerase chain reaction stop assay. Those experimental results indicated that the two complexes can effectively stabilize the G-quadruplex of Pu39. It was found that the complex 2 exhibited greater cytotoxic activity than 1 against human Hela cells and can

enter into Hela cells in a short period of time to effectively induce apoptosis of cells. Further experiments found that complexes 1 and 2 had as potent inhibitory effects on ECV-304 cell migration as suramin. Those noteworthy results provide new insights into the development of anticancer agents for targeting G-quadruplex DNA.

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[457]

**TÍTULO / TITLE:** - Ellagic Acid, a Dietary Polyphenol, Selectively Cytotoxic to HSC-2 Oral Carcinoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):1829-36.

**AUTORES / AUTHORS:** - Weisburg JH; Schuck AG; Reiss SE; Wolf BJ; Fertel SR; Zuckerbraun HL; Babich H

**INSTITUCIÓN / INSTITUTION:** - Department of Biology, Stern College for Women, 245 Lexington Avenue, New York, NY 10016 U.S.A. [weisburg@yu.edu](mailto:weisburg@yu.edu).

**RESUMEN / SUMMARY:** - BACKGROUND: The antiproliferative and apoptotic effects of ellagic acid, a dietary polyphenol, were studied. MATERIALS AND METHODS: The neutral red cytotoxicity assay compared the sensitivities of gingival fibroblasts and HSC-2 oral carcinoma cells to ellagic acid. The ferrous ion oxidation xylenol orange assay and levels of intracellular reduced glutathione were used to assess pro-oxidant nature of ellagic acid. Antioxidant activity was demonstrated in cells co-treated with H<sub>2</sub>O<sub>2</sub> and ellagic acid by 2',7'-dichlorodihydrofluorescein diacetate staining and in cells co-treated with gallic acid and ellagic acid by morphological analysis. Apoptosis was assessed by microscopy, flow cytometry, luminescence, and immunoblotting. RESULTS: Ellagic acid was cytotoxic to carcinoma cells, but not to normal cells. Its pro-oxidant nature was minimal, whereas its antioxidant property was biologically significant. Ellagic acid-treated cells demonstrated apoptotic morphology, induction of apoptosis (flow cytometry), increase in caspase 3/7 activities (luminescence), and activation of caspase 3 and cleavage of poly ADP ribose polymerase (immunoblot). CONCLUSION: Ellagic acid exhibited significant antioxidant, but not pro-oxidant, activity and was selectively cytotoxic to oral carcinoma cells.

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[458]

**TÍTULO / TITLE:** - The effect of liposomal size on the targeted delivery of doxorubicin to Integrin  $\alpha$ v $\beta$ 3-expressing tumor endothelial cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomaterials. 2013 Jul;34(22):5617-27. doi: 10.1016/j.biomaterials.2013.03.094. Epub 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biomaterials.2013.03.094](http://1016/j.biomaterials.2013.03.094)

**AUTORES / AUTHORS:** - Kibria G; Hatakeyama H; Ohga N; Hida K; Harashima H

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Innovative Nanomedicine, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12, Nishi 6, Kita-ku, Sapporo, Hokkaido 060-0812, Japan.

**RESUMEN / SUMMARY:** - Size of the liposomes (LPs) specially governs its biodistribution. In this study, LPs were developed with controlled sizes, where variation in LP size dictates the ligand-receptor interaction, cellular internalization and its distribution within the tumor microenvironment. The therapeutic efficacies of doxorubicin (DOX)-loaded RGD modified small size (approximately 100 nm in diameter, dnm) and large size (approximately 300 dnm) PEGylated LPs (RGD-PEG-LPs) were compared to that of Doxil (a clinically used DOX-loaded PEG-LP, approximately 100 dnm) in DOX resistant OSRC-2 (Renal cell carcinoma, RCC) tumor xenografts. Doxil, which accumulated in tumor tissue via the enhanced permeability and retention (EPR) effect, failed to suppress tumor growth. Small size RGD-PEG-LP, that targets the tumor endothelial cells (TECs) and extravasates to tumor cells, failed to provide anti-tumor effect. Large size RGD-PEG-LP preferentially targets the TECs via minimization of the EPR effect, and significantly reduced the tumor growth, which was exerted through its strong anti-angiogenic activity on the tumor vasculature rather than having a direct effect on DOX resistant RCC. The prepared large size RGD-PEG-LP that targets the TECs via interacting with Integrin  $\alpha v \beta 3$ , is a potentially effective and alternate therapeutic strategy for the treatment of DOX resistant tumor cells by utilizing DOX, in cases where Doxil is ineffective.

[459]

**TÍTULO / TITLE:** - Fixed-dose capecitabine is feasible: results from a pharmacokinetic and pharmacogenetic study in metastatic breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 May;139(1):135-43. doi: 10.1007/s10549-013-2516-z. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2516-z](#)

**AUTORES / AUTHORS:** - Rudek MA; Connolly RM; Hoskins JM; Garrett-Mayer E; Jeter SC; Armstrong DK; Fetting JH; Stearns V; Wright LA; Zhao M; Watkins SP Jr; McLeod HL; Davidson NE; Wolff AC

**INSTITUCIÓN / INSTITUTION:** - Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, CRB1-1M52, Baltimore, MD, 21231, USA, [mrudek2@jhmi.edu](mailto:mrudek2@jhmi.edu).

**RESUMEN / SUMMARY:** - The pro-drug capecitabine is approved for treatment of anthracycline- and paclitaxel-resistant metastatic breast cancer. However, toxicity and large interpatient pharmacokinetic variability occur despite body surface area (BSA)-dosing. We hypothesized that a fixed-dose schedule would

simplify dosing and provide an effective and safe alternative to BSA-based dosing. We conducted an open label, single-arm, two-stage study of oral capecitabine with fixed starting dose (3,000 mg total daily dose in two divided doses x 14 days q21 days) in patients with metastatic breast cancer. We correlated pharmacodynamic endpoints [e.g., efficacy (response) per RECIST and toxicity], adherence and pharmacokinetics/pharmacogenetics. Sample size of 45 patients was required to detect a 25 % response rate from null response rate of 10 % using a Simon two-stage design. Twenty-six patients were enrolled in the first-stage and 21 were evaluable after a median of four cycles of capecitabine. Two thirds of patients received either the same dose or a dose 500 mg lower than what would have been administered with a commonly used 2,000 mg/m<sup>2</sup> BSA-dosing schedule. Eight patients had stable disease but progressed after a median of seven cycles. Despite a clinical benefit rate of 19 %, no RECIST responses were observed following the first stage and the study was closed. Dose-reductions were required for grade 2 hand-foot syndrome (28 %) and vomiting (5 %). Adherence was similar when using both patient-reported and Medication Event Monitoring System methods. High interpatient variability was observed for capecitabine and metabolite pharmacokinetics, but was not attributed to observed pharmacogenetic or BSA differences. Single agent activity of capecitabine was modest in our patients with estrogen receptor-positive or -negative metastatic breast cancer and comparable to recent studies. BSA was not the main source of pharmacokinetic variability. Fixed-dose capecitabine is feasible, and simplifies dosing.

[460]

**TÍTULO / TITLE:** - The chalcone 2'-hydroxy-4',5'-dimethoxychalcone activates death receptor 5 pathway and leads to apoptosis in human nonsmall cell lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - IUBMB Life. 2013 Apr 3. doi: 10.1002/iub.1161.

●●Enlace al texto completo (gratis o de pago) [1002/iub.1161](#)

**AUTORES / AUTHORS:** - Yang L; Su L; Cao C; Xu L; Zhong D; Xu L; Liu X

**INSTITUCIÓN / INSTITUTION:** - Division of Cell Biology, School of Life Sciences, Shandong University, Jinan, People's Republic of China.

**RESUMEN / SUMMARY:** - Natural chalcones have been proved to inhibit cancer cells with therapeutic potential, but the underlying molecular mechanism is still largely unexplored. Here, we identified a novel chalcone, 2'-hydroxy-4',5'-dimethoxychalcone (HDMC) and demonstrated that HDMC induced apoptosis in various nonsmall cell lung cancer cells. Further study showed that HDMC elevated cellular reactive oxygen species (ROS) levels, thus inducing expressions of ATF4 and C/EBP homologous protein (CHOP). Then, death receptor 5 (DR5) was upregulated through ATF4-CHOP axis and eventually resulted in apoptosis. We also found that downregulation of c-FLIPL contributed

to HDMC-induced apoptosis. In conclusion, HDMC induces apoptosis in human nonsmall cell lung cancer cells via activation of DR5 signaling pathway, and ROS-mediated ATF4-CHOP axis is involved in the process. Our results further supported the potential for HDMC to be developed as a new antitumor agent for cancer therapy or chemoprevention. © 2013 IUBMB Life, 2013.

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[461]

**TÍTULO / TITLE:** - Expression of Apoptosis- and Vitamin D Pathway-Related Genes in Hepatocellular Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Digestion. 2013 Apr 27;87(3):176-181.

●●Enlace al texto completo (gratis o de pago) [1159/000348441](http://1159/000348441)

**AUTORES / AUTHORS:** - Fingas CD; Altinbas A; Schlattjan M; Beilfuss A; Sowa JP; Sydor S; Bechmann LP; Ertle J; Akkiz H; Herzer K; Paul A; Gerken G; Baba HA; Canbay A

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, University Hospital, University Duisburg-Essen, Germany.

**RESUMEN / SUMMARY:** - Background/Aims: Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and therapeutic options are scarce. As they might represent future targets for cancer therapy, the expression of apoptosis-related genes in HCC is of particular interest. In this pilot study, we further examined apoptosis-related genes in human HCC and also focused on vitamin D signaling as this might be a regulator of HCC cell apoptosis. Methods: We employed tumor tissue and serum samples from 62 HCC patients as well as 62 healthy controls for these studies. Tissue and serum specimens were analyzed by quantitative RT-PCR, immunohistochemistry and ELISA. Results: In HCC patients the apoptosis marker M30 was found to be elevated and several pro-apoptotic (TRAIL, FasL and FasR) as well as anti-apoptotic genes (Mcl-1 and Bcl-2) were simultaneously upregulated in tumor tissue and especially tumor-surrounding tissue as compared to healthy control livers. Moreover, vitamin D serum levels were decreased in HCC patients whereas vitamin D receptor mRNA expression was increased in tumor tissue and tumor-surrounding tissue as compared to healthy livers. Conclusions: In human HCC, M30 serum levels are elevated indicating an increased cell turnover. Modulation of the vitamin D pathway might be a supportive, pro-apoptotic HCC therapy.

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[462]

**TÍTULO / TITLE:** - High levels of cleaved caspase-3 in colorectal tumour stroma predict good survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 May 28;108(10):2097-105. doi: 10.1038/bjc.2013.166. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.166](https://doi.org/10.1038/bjc.2013.166)

**AUTORES / AUTHORS:** - Noble P; Vyas M; Al-Attar A; Durrant S; Scholefield J; Durrant L

**INSTITUCIÓN / INSTITUTION:** - Academic Department of Clinical Oncology, University of Nottingham, City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK.

**RESUMEN / SUMMARY:** - Aim:The primary aim was to determine the prognostic significance of apoptosis in colorectal tumour cells and tumour-associated stroma. A secondary aim was to determine whether apoptosis was related to immune surveillance. Methods:Immunohistochemistry was performed using monoclonal antibodies recognising cleaved caspase-3 (CC3), cleaved poly (ADP-ribose) polymerase (PARP), p53, Bcl2, MHC-II, B cells (CD16), macrophages (CD68) and T cells (CD3), on a tissue microarray of 462 colorectal tumours. Results:Kaplan-Meier analysis demonstrated that patients with high expression of CC3 in the tumour or CC3 or cleaved PARP in tumour-associated stroma have a good prognosis. This suggests that tumour stroma is promoting tumourigenesis and that high levels of death within the stroma breaks this link. CC3 levels in the tumour correlated with cleaved PARP and MHC-II expression but not with CD16, CD68, CD3, p53 or Bcl2 expression. CC3 levels on tumour-associated stroma also correlated with cleaved PARP and MHC-II expression but not with CD16, CD68, CD3, p53 or Bcl2 expression. Tumour cells express MHC-II in response to IFN-gamma, suggesting that this may be one of the initiators of apoptosis within the good prognosis tumours. Although 73% of the MHC-II-positive tumour had high levels of apoptosis, many tumours had high levels of apoptosis in the absence of MHC-II, implying that this is only one of many causes of apoptosis within tumours. On multivariate analysis, using Cox's proportional hazards model, tumour stage, vascular invasion and expression of CC3 in tumour-associated stroma were shown to be independent markers of prognosis. Conclusion:This study shows that a high level of apoptosis within colorectal tumour-associated stroma is an independent marker of good prognosis.

[463]

**TÍTULO / TITLE:** - PF-04691502 triggers cell cycle arrest, apoptosis and inhibits the angiogenesis in hepatocellular carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Toxicol Lett. 2013 Apr 29;220(2):150-156. doi: 10.1016/j.toxlet.2013.04.018.

●●Enlace al texto completo (gratis o de pago)

[1016/j.toxlet.2013.04.018](https://doi.org/10.1016/j.toxlet.2013.04.018)

**AUTORES / AUTHORS:** - Wang FZ; Peng-Jiao; Yang NN; Chuang-Yuan; Zhao YL; Liu QQ; Fei HR; Zhang JG

**INSTITUCIÓN / INSTITUTION:** - School of Biological Science, Taishan Medical University, Chang Cheng Road, Taian 271016, PR China; Key Laboratory of Brain Microcirculation in Universities of Shandong, Taishan Medical University, Chang Cheng Road, Taian 271016, PR China.

**RESUMEN / SUMMARY:** - Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality in the world. The aim of the present study is to determine the antitumor effect of PF-04691502, a potent inhibitor of PI3K and mTOR kinases, on the apoptosis and angiogenesis of the hepatoma cancer cells. Our results indicate that treatment of cancer cells with PF-04691502 reduces cell viability and inhibits cell growth in a dose-dependent manner. PF-04691502 triggers apoptosis via a mitochondrial pathway, accompanied by activation of caspase-3, caspase-9, and poly(ADP-ribose) polymerase (PARP). Pre-treatment of hepatoma cells with the caspase-3 inhibitor (z-DEVD-fmk) blocks the PF-04691502-induced death of these cells. In addition, growth factors-induced tube formation and the migration of HUVECs are markedly inhibited by PF-04691502 treatment. The mechanisms of anti-angiogenesis of PF-04691502 are associated with inhibiting the expression of VEGF and HIF-1 $\alpha$ . Based on the overall results, we suggest that PF-04691502 reduces hepatocellular carcinoma cell viability, induces cell apoptosis, and inhibits cell growth and tumor angiogenesis, implicating its potential therapeutic value in the treatment of HCC.

[464]

**TÍTULO / TITLE:** - Anastrozole and RU486: Effects on estrogen receptor alpha and Mucin 1 expression and correlation in the MCF-7 breast cancer cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Histochem. 2013 May 20. pii: S0065-1281(13)00078-0. doi: 10.1016/j.acthis.2013.04.006.

●●Enlace al texto completo (gratis o de pago)

[1016/j.acthis.2013.04.006](#)

**AUTORES / AUTHORS:** - Gil JF; Augustine TN; Hosie MJ

**INSTITUCIÓN / INSTITUTION:** - School of Anatomical Sciences, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown 2193, Johannesburg, South Africa.

**RESUMEN / SUMMARY:** - Anastrozole and RU486 are shown to reduce hormone-responsive breast cancer progression when used as adjuvant treatments to surgical intervention, however, a high incidence of cancer recurrence remains. Estrogen receptor alpha (ER $\alpha$ ) and Mucin 1 (MUC1), a glycoprotein, are both implicated in breast cancer progression. We assessed whether Anastrozole and RU486 treatment affects the expression of, and relationship between, ER $\alpha$  and MUC1 in the ER $\alpha$ + MUC1+ MCF-7 breast cancer

cell line. MCF-7 cells, treated with physiological concentrations of either Anastrozole or RU486 for 18h or 72h, were subjected to immunolocalization of both markers. CellProfiler software was used to quantify intensity for statistical analyses. ERalpha expression increased at both time periods following treatment. MUC1 expression increased with RU486-treatment at both times, whereas Anastrozole induced increased MUC1 expression at 72h only. The biomarkers demonstrated increased point association at 72h within treatment groups despite MUC1 diverging from correlation with ERalpha. We propose that tumor progression is independent of MUC1 and ERalpha correlation. These preliminary results indicate that withdrawal of adjuvant treatment may result in residual cell populations expressing increased ERalpha and MUC1. This phenotype may allow enhanced estrogenic and metastatic capacity influencing cancer recurrence, a hypothesis we are investigating further.

[465]

**TÍTULO / TITLE:** - Gene methylation in rectal cancer: Predictive marker of response to chemoradiotherapy?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Physiol. 2013 May 23. doi: 10.1002/jcp.24405.

●●Enlace al texto completo (gratis o de pago) [1002/jcp.24405](#)

**AUTORES / AUTHORS:** - Molinari C; Casadio V; Foca F; Zingaretti C; Giannini M; Avanzolini A; Lucci E; Saragoni L; Passardi A; Amadori D; Calistri D; Zoli W

**INSTITUCIÓN / INSTITUTION:** - Biosciences Laboratory, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Italy.

**RESUMEN / SUMMARY:** - Although numerous studies have focused on the link between CpG island methylator phenotypes and the development of colorectal cancer, few studies have dealt specifically with methylation profiling in rectal cancer and its role in predicting response to neoadjuvant chemoradiotherapy (NCRT). We characterized methylation profiles in normal and neoplastic tissue samples from patients with rectal cancer and assessed the role of this molecular profile in predicting chemoradioactivity. We evaluated 74 pretreatment tumor samples and 16 apparently normal tissue biopsies from rectal cancer patients submitted to NCRT. The methylation profile of 24 different tumor suppressor genes was analyzed from FFPE samples by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). Methylation status was studied in relation to tissue type and clinical pathological parameters, in particular, pathological response evaluated by tumor regression grade (TRG). ESR1, CDH13, RARB, IGSF4 and APC genes showed high methylation levels in tumor samples (range 18.92-49.77) with respect to normal tissue. Methylation levels of the remaining genes were low and similar in both normal (range 1.91-14.56) and tumor tissue (range 1.84-11). Analysis of the association between methylation and response to therapy in tumor samples showed that only TIMP3 methylation status differed significantly within the four

TRG classes (ANOVA,  $P < 0.05$ ). Results from the present explorative study suggest that quantitative epigenetic classification of rectal cancer by MS-MLPA clearly distinguishes tumor tissue from apparently normal mucosa. Conversely, with the exception of TIMP3 gene, the methylation of selected genes does not seem to correlate with response to NCRT. *J. Cell. Physiol.* © 2013 Wiley Periodicals, Inc.

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[466]

**TÍTULO / TITLE:** - Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras/NFkappaB dependent manner.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Cancer Lett.* 2013 Mar 31. pii: S0304-3835(13)00255-3. doi: 10.1016/j.canlet.2013.03.025.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.03.025](http://1016/j.canlet.2013.03.025)

**AUTORES / AUTHORS:** - Dixit D; Ghildiyal R; Anto NP; Ghosh S; Sharma V; Sen E

**INSTITUCIÓN / INSTITUTION:** - National Brain Research Centre, Manesar, Haryana 122 050, India.

**RESUMEN / SUMMARY:** - Since Shh pathway effector, Gli1, is overexpressed in gliomas, we investigated the effect of novel Shh inhibitor SANT-1 on glioma cell viability. Though SANT-1 failed to induce apoptosis, it reduced proliferation of glioma stem-like cells. Apart from canonical Shh cascade, Gli1 is also induced by non-canonical pathways including NFkappaB. Therefore, a combinatorial strategy with Ras/NFkappaB inhibitor, Guggulsterone, was employed to enhance effectiveness of SANT-1. Guggulsterone inhibited Ras and NFkappaB activity and sensitized cells to SANT-1 induced apoptosis via intrinsic apoptotic mechanism. Inhibition of either Ras or NFkappaB activity was sufficient to sensitize cells to SANT-1. Guggulsterone induced ERK activation also contributed to Caspase-9 activation. Since SANT-1 and Guggulsterone differentially target stem-like and non-stem glioma cells respectively, this combination warrants investigation as an effective anti-glioma therapy.

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[467]

**TÍTULO / TITLE:** - The prevalence and prognostic significance of KRAS mutation in bladder cancer, chronic myeloid leukemia and colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Mol Biol Rep.* 2013 Jun;40(6):4109-14. doi: 10.1007/s11033-013-2512-8. Epub 2013 May 3.

●●Enlace al texto completo (gratis o de pago) [1007/s11033-013-2512-](http://1007/s11033-013-2512-8)

[8](#)

**AUTORES / AUTHORS:** - Ouerhani S; Bougatef K; Soltani I; Elgaaied AB; Abbes S; Menif S

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Molecular and Cellular Haematology, Pasteur Institute of Tunis, University of Tunis El Manar, Tunis, Tunisia, [slah\\_mekni@yahoo.fr](mailto:slah_mekni@yahoo.fr).

**RESUMEN / SUMMARY:** - Mutations in the KRAS gene have been shown to play a key role in the pathogenesis of a variety of human tumours. However the mutational spectrum of KRAS gene differs by organ site. In this study, we have analysed the mutational spectrum of KRAS exon 1 in bladder tumours, colorectal cancer (CRC) and chronic myeloid leukemia (CML). A total of 366 patients were included in the present study (234 bladder tumours, 48 CRC and 84 CML). The KRAS mutations are absent in BCR/ABL1 positive CML. This result suggests that BCR/ABL1 fusion gene and KRAS mutations were mutually exclusive. The frequency of KRAS mutations in bladder cancer was estimated at 4.27 %. All of mutations were found in codon 12 and 90 % of them were detected in advanced bladder tumours. However the correlation between KRAS mutations and tumour stage and grade does not report a statistical significant association. The KRAS mutations occur in 35.41 % of patients with CRC. The most frequent mutations were G12C, G12D and G13D. These mutations were significantly correlated with histological differentiation of CRC ( $p = 0.024$ ). Although the high frequency of KRAS in CRC in comparison to bladder cancer, these two cancers appear to have the same mutational spectrum ( $p > 0.05$ ).

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[468]

**TÍTULO / TITLE:** - Extensive tracheal necrosis after treatment of anaplastic thyroid cancer with vascular endothelial growth factor inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Thorac Surg. 2013 Jun;95(6):2181. doi: 10.1016/j.athoracsur.2012.09.081.

●●Enlace al texto completo (gratis o de pago)

[1016/j.athoracsur.2012.09.081](http://1016/j.athoracsur.2012.09.081)

**AUTORES / AUTHORS:** - Gonfiotti A; Jaus MO; Barale D; Macchiarini P

**INSTITUCIÓN / INSTITUTION:** - European Center of Thoracic Research, University Hospital Careggi, Florence, Italy.

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[469]

**TÍTULO / TITLE:** - B7-H4 enhances oncogenicity and inhibits apoptosis in pancreatic cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Tissue Res. 2013 May 10.

●●Enlace al texto completo (gratis o de pago) [1007/s00441-013-1640-](http://1007/s00441-013-1640-8)

[8](#)

**AUTORES / AUTHORS:** - Qian Y; Hong B; Shen L; Wu Z; Yao H; Zhang L  
**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Institute of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, 310003, Hangzhou, China, [qianyunm@hotmail.com](mailto:qianyunm@hotmail.com).  
**RESUMEN / SUMMARY:** - B7-H4 is expressed in a variety of tumor cells and functions as a negative regulator of T cells. However, clarification is needed as to whether B7-H4 mediates tumorigenesis through mechanisms, such as apoptosis, in addition to mediating tumor immune escape. We investigate the mechanisms involved in enhanced oncogenicity and the inhibition of apoptosis by B7-H4 in pancreatic cancer cells. Short interfering RNAs (siRNAs) specific for B7-H4 were evaluated for their ability to knockdown B7-H4 mRNA and protein expression in pancreatic cancer cells and the most effective siRNA was selected for investigating the effect of B7-H4 gene silencing in a number of functional assays. The inhibition of B7-H4 increased cell-cell adhesion and decreased the formation of pseudopodia. It also increased the expression of E-cadherin and decreased the expression of vimentin and CD44. B7-H4 siRNA inhibited cell proliferation, colony formation and migration of pancreatic cancer cells. Moreover, increased apoptosis in pancreatic cancer cells following B7-H4 silencing was demonstrated in vitro by using flow cytometry and in a xenograft tumor model and was associated with increased caspase activity and decreased Erk1/2 phosphorylation both in vitro and in vivo. Loss of B7-H4 function thus prevents tumor growth through many processes, including the induction of apoptosis and inhibition of the Erk1/2 signaling pathway indicating that B7-H4 is a cancer promoter and a potentially important therapeutic target. B7-H4 inhibition might offer an exciting opportunity to inhibit the progression of human pancreatic cancers.

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[470]

**TÍTULO / TITLE:** - Combination of Azacitidine and Lenalidomide in Myelodysplastic Syndromes or acute Myeloid Leukemia-a wise Liaison?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leukemia. 2013 May 6. doi: 10.1038/leu.2013.140.

●●Enlace al texto completo (gratis o de pago) [1038/leu.2013.140](http://1038/leu.2013.140)

**AUTORES / AUTHORS:** - Platzbecker U; Germing U

**INSTITUCIÓN / INSTITUTION:** - [1] Medical Clinic I, University Hospital, Technical University, Dresden, Germany [2] German MDS Study Group.

**RESUMEN / SUMMARY:** - Treatment options for older patients with advanced myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) are limited and the prognosis remains poor, thereby warranting development of novel therapies. Aberrant epigenetic modifications, including altered DNA methylation, seem to contribute to the pathogenesis of these patients. In fact, hypomethylating agents (HMA) like azacitidine have been successfully used in

clinical trials and achieved approval from health authorities. There is now growing evidence suggesting that the combination of drugs with different mechanisms of action might offer a potential benefit to these patients. This is especially done with the intention to synergize the positive effects of each drug on the defective hematopoiesis while sparing potential side effects and toxicities. Combination of HMA with histone deacetylase inhibitors, although mechanistically very tempting, have not yielded convincing improvement of the results in the majority of trials compared to single agent HMA treatment. Currently, combination therapies of azacitidine with lenalidomide appear to be promising thus making them an appealing option for treatment in these patients. Leukemia advance online publication, 28 May 2013; doi:10.1038/leu.2013.140.

[471]

**TÍTULO / TITLE:** - Male breast cancer and 5-alpha reductase inhibitors, finasteride and dutasteride.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Urol. 2013 May 9. pii: S0022-5347(13)04325-5. doi: 10.1016/j.juro.2013.04.132.

●●Enlace al texto completo (gratis o de pago) [1016/j.juro.2013.04.132](#)

**AUTORES / AUTHORS:** - Bird ST; Brophy JM; Hartzema AG; Delaney JA; Etminan M

**INSTITUCIÓN / INSTITUTION:** - Department of Health and Human Services / Food and Drug Administration / Center for Drug Evaluation and Research (CDER) / Office of Pharmacovigilance and Epidemiology / Office of Surveillance and Epidemiology / Department of Epidemiology, 10903 New Hampshire Avenue, Silver Spring, MD, USA; Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida, 101 S. Newell Drive (HPNP), PO Box 100496, Gainesville FL, USA.

**RESUMEN / SUMMARY:** - PURPOSE: To examine the association between 5-alpha-reductase inhibitors (5ARI) and male breast cancer. MATERIALS AND METHODS: Study participants were men aged 40-85 years, having prescription and medical coverage, and enrolled in the United States IMS claims-database between 2001-2009. Cases required a primary breast cancer diagnosis (ICD-9-CM 175.X) on 2 different dates and either a procedural code for a mastectomy or a lumpectomy/partial mastectomy with evidence of continuous care (radiation/chemotherapy or diagnoses in  $\geq 2$  months). Eligible controls were aged within 5 years and had duration of prior healthcare enrollment within 6 weeks. Risk set sampling selected 20 controls per case. We assessed the rate ratio (RR) for male breast cancer with 5ARI exposure using conditional logistic regression. Analyses were stratified by duration of healthcare enrollment prior to diagnosis ( $\geq 1$  year,  $\geq 2$  years, and  $\geq 3$  years) each incremental 180 and 365 days of cumulative 5ARI exposure, and period-specific timeframes prior to

diagnosis(years 1, 2, and 3). RESULTS: We identified 339 breast cancer cases matched to 6,780 controls. No statistically significant associations were observed between 5ARIs and breast cancer, regardless of exposure assessment prior to index date [ $\geq 1$  year (RR 0.70 95%CI: 0.34-1.45),  $\geq 2$  years (RR 0.59 95%CI: 0.24-1.48), or  $\geq 3$  years (RR 0.75 95%CI: 0.27-2.10)]. Each subsequent 180 days [RR 1.02 95%CI: 0.67-1.53] and 365 days [RR 1.03 95%CI: 0.45-2.37] of cumulative 5ARI therapy and period-specific RRs also observed null associations. CONCLUSIONS: The lack of an association in our study suggests breast cancer development should not influence prescribing of 5ARI therapy.

[472]

**TÍTULO / TITLE:** - Indole-3-carbinol inhibits cell proliferation and induces apoptosis in Hep-2 laryngeal cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):227-33. doi: 10.3892/or.2013.2411. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2411](#)

**AUTORES / AUTHORS:** - Wang YQ; Chen C; Chen Z; Xu Y; Wang Y; Xiao BK; Chen SM; Tao ZZ

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology, Head and Neck Surgery, Renmin Hospital of Wuhan University, Wuhan 430060, P.R. China.

**RESUMEN / SUMMARY:** - Indole-3-carbinol (I3C) is an active component of cruciferous vegetables and markedly inhibits the growth of a variety of tumors. However, its role in laryngeal cancer remains obscure. The aim of the present study was to elucidate the possible mechanisms whereby I3C influences Hep-2 laryngeal cancer cell proliferation and apoptosis. Treatment with I3C dose-dependently and significantly inhibited Hep-2 cell proliferation, and at doses of 100 and 150 microM, I3C induced cell morphological changes and promoted apoptosis. Following treatment of Hep-2 cells with I3C, we found that the protein expression of phosphatidylinositol-3-kinase (PI3K) p110alpha, PI3K p110beta, PI3K class III, p-PDK1, Akt, p-Akt and the downstream signaling proteins p-c-Raf and GSK3-beta were significantly downregulated. Additionally, tumor-bearing mouse models were constructed using BALB/c nude mice. The mice were subdivided into groups: pretreated with I3C, or treated with I3C or an untreated control group. After 8 weeks, mice pretreated or treated with I3C developed smaller tumors compared to the untreated control group, and the protein expression of PI3K p110alpha, PI3K class III, Akt, p-Akt and the downstream signaling proteins p-c-Raf and GSK3-beta in the tumors were significantly downregulated. Furthermore, no harmful side effect were observed in the heart, liver and kidney of the I3C-treated nude mice. In conclusion, I3C inhibited proliferation and induced the apoptosis of laryngeal tumor cells both in vivo and in vitro, and exhibited low toxicity to normal cells. The inhibitory effects

noted with I3C treatment may depend on decreased phosphatidylinositol-3 kinase/serine-threonine kinase (PI3K/Akt) expression. This approach may be applied to the clinical treatment of laryngeal tumors and in drug screening.

[473]

**TÍTULO / TITLE:** - SUOX is a Promising Diagnostic and Prognostic Biomarker for Hepatocellular Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hepatol. 2013 May 8. pii: S0168-8278(13)00283-3. doi: 10.1016/j.jhep.2013.04.028.

●●Enlace al texto completo (gratis o de pago) [1016/j.jhep.2013.04.028](#)

**AUTORES / AUTHORS:** - Jin GZ; Yu WL; Dong H; Zhou WP; Gu YJ; Yu H; Yu H; Lu XY; Xian ZH; Liu YK; Cong WM; Wu MC

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, 200438, China.

**RESUMEN / SUMMARY:** - BACKGROUND & AIMS: To investigate diagnostic and prognostic values of sulfite oxidase (SUOX) in patients with hepatocellular carcinoma (HCC) who underwent curative resection. METHODS: We investigated immunohistochemically the expression dynamics of SUOX, aldo-ketoreductase family 1 member B10 (AKR1B10) and CD34 at different stages of HCC. The differential diagnostic performance of three markers or their combinations in high-grade dysplastic nodules (HGDNs) and well-differentiated small HCC (WD-sHCC) were investigated by logistic regression models and validated in an independent testing set. Overall survival (OS) and time to recurrence (TTR) were evaluated in 300 patients with HCC as the testing cohort, and validated in 198 patients with HCC. RESULTS: SUOX was decreased and AKR1B10 and CD34 were increased with the stepwise progression of hepatocarcinogenesis. For differential diagnosis of WD-sHCC from HGDNs, the sensitivity and specificity of the SUOX+AKR1B10+CD34 combination for WD-sHCC detection were 93.8% and 95.2%, respectively, and overall accuracy was much higher than any of the three individual markers and two marker combinations. In addition, SUOX, but not AKR1B10 and CD34, was an independent prognostic factor for OS and TTR, and showed better correlation with OS and TTR if combined with serum alpha-fetoprotein (AFP) for both the testing and validation cohorts. CONCLUSIONS: SUOX+AKR1B10+CD34 combination could make a substantial contribution to hepatic immunopathological diagnosis to distinguish WD-sHCC from HGDNs. Meanwhile, SUOX combined with serum AFP may predict postoperative outcome and tumor recurrence risk.

[474]

**TÍTULO / TITLE:** - Overexpression of the chromatin remodeler death-domain-associated protein in prostate cancer is an independent predictor of early prostate-specific antigen recurrence.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Pathol. 2013 May 2. pii: S0046-8177(13)00082-8. doi: 10.1016/j.humpath.2013.01.022.

●●Enlace al texto completo (gratis o de pago)

[1016/j.humpath.2013.01.022](#)

**AUTORES / AUTHORS:** - Tsourlakis MC; Schoop M; Plass C; Huland H; Graefen M; Steuber T; Schlomm T; Simon R; Sauter G; Sirma H; Minner S

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, University Medical Center Hamburg-Eppendorf, D-20246 Hamburg, Germany.

**RESUMEN / SUMMARY:** - Molecular markers reliably predicting the aggressiveness of prostate cancer are currently lacking. Death-domain-associated protein (DAXX) has been implicated in the regulation of chromatin remodeling, transcription, and apoptosis that are integral to oncogenesis and cancer progression. DAXX expression was analyzed by immunohistochemistry on a tissue microarray containing 7478 prostate cancer specimens. Results were compared with tumor phenotype, biochemical recurrence, and v-ets erythroblastosis virus E26 oncogene homolog (ERG) status. DAXX expression was predominantly seen in the nucleus. DAXX expression was detectable in 4609 (80.6%) of 5718 interpretable cancers and considered strong in 5.9%, moderate in 45.8%, and weak in 28.9%. Strong DAXX expression was associated with both transmembrane protease, serine 2 (TMPRSS2)/ERG rearrangement and ERG expression ( $P < .0001$  each). Strong DAXX expression was tightly linked to high Gleason grade, advanced pT stage, increased cell proliferation index, and early prostate-specific antigen recurrence ( $P < .0001$  each). The prognostic role of DAXX expression was independent of Gleason grade, pT stage, and pN stage. Our study establishes DAXX as a novel independent prognosticator in prostate cancer and suggests an important role of DAXX expression for both prostate cancer development and progression. Furthermore, DAXX appears to exert biologically different effects in ERG-positive and ERG-negative prostate cancers.

[475]

**TÍTULO / TITLE:** - The role of CDK1 in apoptin-induced apoptosis in hepatocellular carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):253-9. doi: 10.3892/or.2013.2426. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2426](#)

**AUTORES / AUTHORS:** - Zhao J; Han SX; Ma JL; Ying X; Liu P; Li J; Wang L; Zhang Y; Ma J; Zhang L; Zhu Q

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, The First Affiliated Hospital, Xi'an Jiaotong University Medical college, Xi'an, Shaanxi 710061, P.R. China.

**RESUMEN / SUMMARY:** - Apoptin, a small protein derived from the chicken anemia virus, specifically induces apoptosis in transformed cells or tumor cells but not in normal cells. Thus, apoptin is involved in a general, tumor-specific pathway. Apoptin-induced apoptosis presumably requires additional interaction partners that activate specific signaling pathways in cancer cells. A number of molecules interact with apoptin and play an important role in the nuclear localization of apoptin or its tumor-selective cytotoxicity. Our data indicated that apoptin selectively kills HepG2 hepatocellular carcinoma (HCC) cells but has no effect on the normal liver cell line HL-7702. Analyses of human HCC tissue samples confirmed that CDK1 (cyclin-dependent kinase 1) activity was detected in primary malignancies but not in healthy paraneoplastic tissues. shRNA knockdown of CDK1 significantly reduced the tumor-specific killing effects of apoptin, suggesting that CDK1 plays an important role in the regulation of apoptin-induced apoptosis. Furthermore, the majority of apoptin translocated to the cytoplasm from the nucleus after knockdown of CDK1. Collectively, our results revealed for the first time that apoptin interacts with CDK1 in the complex process of tumorigenesis. The link between CDK1 and apoptin may be a novel cellular signaling pathway to modulate apoptosis in cancer; therefore, apoptin may have pharmacological potential to be directly employed for cancer therapy.

[476]

**TÍTULO / TITLE:** - Basic mechanisms of therapeutic resistance to radiation and chemotherapy in lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer J. 2013 May-Jun;19(3):200-7. doi: 10.1097/PPO.0b013e318292e4e3.

●●Enlace al texto completo (gratis o de pago)

[1097/PPO.0b013e318292e4e3](#)

**AUTORES / AUTHORS:** - Willers H; Azzoli CG; Santivasi WL; Xia F

**INSTITUCIÓN / INSTITUTION:** - From the \*Department of Radiation Oncology, and daggerDivision of Hematology/Oncology, Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; and double daggerDepartment of Radiation Oncology, College of Medicine, Ohio State University, Columbus, OH.

**RESUMEN / SUMMARY:** - In recent years, there have been multiple breakthroughs in our understanding of lung cancer biology. Despite significant advances in molecular targeted therapies, DNA-damaging cytotoxic therapies will remain the mainstay of lung cancer management for the near future. Similar to the concept of personalized targeted therapies, there is mounting evidence that

perturbations in DNA repair pathways are common in lung cancers, altering the resistance of the affected tumors to many chemotherapeutics as well as radiation. Defects in DNA repair may be due to a multitude of mechanisms including gene mutations, epigenetic events, and alterations in signal transduction pathways such as epidermal growth factor receptor and phosphoinositide 3-kinase/AKT. Functional biomarkers that assess the subcellular localization of central repair proteins in response to DNA damage may prove useful for individualization of cytotoxic therapies including poly(adenosine diphosphate-ribose) polymerase inhibitors. A better mechanistic understanding of cellular sensitivity and resistance to DNA damaging agents should facilitate the development of novel, individualized treatment approaches. Absolute resistance to radiation therapy, however, does not exist. To some extent, radiation therapy will always have to remain unselective and indiscriminant to eradicate persistent, drug-resistant tumor stem cell pools.

[477]

**TÍTULO / TITLE:** - Targeted manipulation of apoptotic pathways by using High Intensity Focused Ultrasound in cancer treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Apr 21. pii: S0304-3835(13)00350-9. doi: 10.1016/j.canlet.2013.04.016.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.04.016](http://1016/j.canlet.2013.04.016)

**AUTORES / AUTHORS:** - Saliev T; Feril LB Jr; Nabi G; Melzer A

**INSTITUCIÓN / INSTITUTION:** - Institute for Medical Science and Technology, University of Dundee, Wilson House, 1 Wurzburg Loan, Dundee DD2 1FD, United Kingdom. Electronic address: [tim.saliev@gmail.com](mailto:tim.saliev@gmail.com).

**RESUMEN / SUMMARY:** - Apoptosis, or programmed cell death, is a mechanism of cell death, which has been exploited for the treatment of cancers over the past few years. The understanding of apoptosis pathways (intrinsic and extrinsic) has led to discovery of treatment strategies which selectively target the cancer cells and spare the normal ones. This article reviews the current understanding of the apoptotic pathways which are utilized for targeting cancer cells using High Intensity Focused Ultrasound (HIFU).

[478]

**TÍTULO / TITLE:** - DICO, a novel nonaromatic B-ring flavonoid, induces G2/M cell cycle arrest and apoptosis in human hepatoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Food Chem Toxicol. 2013 Jul;57:322-9. doi: 10.1016/j.fct.2013.03.032. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.03.032](http://1016/j.fct.2013.03.032)

**AUTORES / AUTHORS:** - Zhou D; Wei A; Cao C; Ruan J

**INSTITUCIÓN / INSTITUTION:** - Beijing Institute of Biotechnology, Beijing 100000, China; Postdoctoral Programme, Mayinglong Pharmaceutical Group Co. Ltd., Wuhan 430030, China.

**RESUMEN / SUMMARY:** - DICO was a novel nonaromatic B-ring flavonoid obtained from *Macrothelypteris torresiana*. In the present work, we investigated the antitumor activity and the antineoplastic mechanism of DICO. Our study showed that DICO inhibited the growth of HepG2 cells in dose and time-dependent manners. As well as DICO induced G2/M cell cycle arrest and apoptosis via a ROS-mediated mitochondrial pathway. Western blot assay demonstrated that DICO decreased Bcl-2 level and induced Bax translocation to cause cytochrome c release. Subsequently, caspase-9 and caspase-3 were activated. Meanwhile, the alterations of cyclin A and B1, p-CDK1 and p-cdc25c levels were also observed in response to DICO treatment. Taken together, DICO displayed a significant antitumor effect through G2/M cell cycle arrest and apoptosis induction, which suggested DICO might have therapeutic potential against tumors.

[479]

**TÍTULO / TITLE:** - The influence of the penetrating peptide iRGD on the effect of paclitaxel-loaded MT1-AF7p-conjugated nanoparticles on glioma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Biomaterials*. 2013 Jul;34(21):5138-48. doi: 10.1016/j.biomaterials.2013.03.036. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biomaterials.2013.03.036](#)

**AUTORES / AUTHORS:** - Gu G; Gao X; Hu Q; Kang T; Liu Z; Jiang M; Miao D; Song Q; Yao L; Tu Y; Pang Z; Chen H; Jiang X; Chen J

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Smart Drug Delivery, Ministry of Education & PLA, School of Pharmacy, Fudan University, Lane 826, Zhangheng Road, Shanghai 201203, PR China.

**RESUMEN / SUMMARY:** - Low permeability across the blood-brain tumor barrier (BTB) and poor penetration into the glioma parenchyma represent key obstacles for anti-glioblastoma drug delivery. In this study, MT1-AF7p peptide, which presents high binding affinity to membrane type-1 matrix metalloproteinase (MT1-MMP) that over-expressed on both angiogenic blood vessels and glioma cells, was employed to decorate the paclitaxel-loaded PEG-PLA nanoparticles (MT1-NP-PTX) to mediate glioblastoma targeting. Tumor-homing and penetrating peptide iRGD was co-administrated to further facilitate nanoparticles extravasation from the tumor vessels and penetration into the glioma parenchyma. MT1-NP-PTX showed satisfactory encapsulated efficiency, loading capacity and size distribution. In C6 glioma cells, MT1-NP was found to exhibit significantly enhanced cellular accumulation than that of unmodified NP

via both energy-dependent macropinocytosis and lipid raft-mediated endocytosis. The anti-proliferative and apoptosis-induction activity of PTX was significantly enhanced following its encapsulation in MT1-NP. In vivo imaging and glioma distribution together confirmed that MT1-AF7p functionalization and iRGD co-administration significantly improved the nanoparticles extravasation across BTB and accumulation in glioma parenchyma. Furthermore, in vitro C6 glioma spheroid assays evidenced that MT1-NP effectively penetrated into the glioma spheroids and significantly improved the growth inhibitory effects of loaded PTX on glioma spheroids. More importantly, the median survival time of those nude mice bearing intracranial C6 glioma received MT1-NP-PTX and iRGD combination regimen was 60 days, significantly longer than that of other groups. The findings suggested that the BTB/glioma cells dual-targeting DDS co-administrated with iRGD peptide might provide a both practical and feasible solution to highly efficient anti-glioblastoma drug delivery.

[480]

**TÍTULO / TITLE:** - Ellagic acid induces apoptosis in tsgH8301 human bladder cancer cells through the endoplasmic reticulum stress- and mitochondria-dependent signaling pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Environ Toxicol. 2013 Mar 30. doi: 10.1002/tox.21857.

●●Enlace al texto completo (gratis o de pago) [1002/tox.21857](#)

**AUTORES / AUTHORS:** - Ho CC; Huang AC; Yu CS; Lien JC; Wu SH; Huang YP; Huang HY; Kuo JH; Liao WY; Yang JS; Chen PY; Chung JG

**INSTITUCIÓN / INSTITUTION:** - Department of Biological Science and Technology, China Medical University, Taichung, 404, Taiwan.

**RESUMEN / SUMMARY:** - To investigate the effects of ellagic acid on the growth inhibition of TSGH8301 human bladder cancer cells in vitro, cells were incubated with various doses of ellagic acid for different time periods. The phase-contrast microscope was used for examining and photographing the morphological changes in TSGH8301 cells. Flow cytometric assay was used to measure the percentage of viable cells, cell cycle distribution, apoptotic cells, ROS, mitochondrial membrane potential (DeltaPsim), Ca<sup>2+</sup>, caspase-9 and -3 activities in TSGH8301 cells after exposure to ellagic acid. Western blotting was used to examine the changes of cell cycle and apoptosis associated proteins levels. Results indicated that ellagic acid induced morphological changes, decreased the percentage of viable cells through the induction of G0/G1 phase arrest and apoptosis, and also showed that ellagic acid promoted ROS and Ca<sup>2+</sup> productions and decreased the level of DeltaPsim and promoted activities of caspase-9 and -3. The induction of apoptosis also confirmed by annexin V staining, comet assay, DAPI staining and DNA gel electrophoresis showed that ellagic acid induced apoptosis and DNA damage in TSGH8301 cells. Western blotting assay showed that ellagic acid promoted p21, p53 and decreased

CDC2 and WEE1 for leading to G0/G1 phase arrest and promoting BAD expression, AIF and Endo G, cytochrome c, caspase-9 and -3 for leading to apoptosis in TSGH8301 cells. On the basis of these observations, we suggest that ellagic acid induced cytotoxic effects for causing a decrease in the percentage of viable cells via G0/G1 phase arrest and induction of apoptosis in TSGH8301 cells. © 2013 Wiley Periodicals, Inc. Environ Toxicol, 2013.

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[481]

**TÍTULO / TITLE:** - A novel role of ribonuclease inhibitor in regulation of epithelial-to-mesenchymal transition and ILK signaling pathway in bladder cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Tissue Res. 2013 May 24.

●●Enlace al texto completo (gratis o de pago) [1007/s00441-013-1638-](#)

[2](#)

**AUTORES / AUTHORS:** - Yao X; Li D; Xiong DM; Li L; Jiang R; Chen JX

**INSTITUCIÓN / INSTITUTION:** - Department of Cell Biology and Genetics, Chongqing Medical University, 1 Yixueyuan Road, Yuzhong District, Chongqing, 400016, People's Republic of China.

**RESUMEN / SUMMARY:** - Human ribonuclease inhibitor (RI) is a cytoplasmic acidic protein possibly involved in biological functions other than the inhibition of RNase A and angiogenin activities. We have previously shown that RI can inhibit growth and metastasis in some cancer cells. Epithelial-mesenchymal transition (EMT) is regarded as the beginning of invasion and metastasis and has been implicated in the metastasis of bladder cancer. We therefore postulate that RI regulates EMT of bladder cancer cells. We find that the over-expression of RI induces the up-regulation of E-cadherin, accompanied with the decreased expression of proteins associated with EMT, such as N-cadherin, Snail, Slug, vimentin and Twist and of matrix metalloprotein-2 (MMP-2), MMP-9 and Cyclin-D1, both in vitro and in vivo. The up-regulation of RI inhibits cell proliferation, migration and invasion, alters cell morphology and adhesion and leads to the rearrangement of the cytoskeleton in vitro. We also demonstrate that the up-regulation of RI can decrease the expression of integrin-linked kinase (ILK), a central component of signaling cascades controlling an array of biological processes. The over-expression of RI reduces the phosphorylation of the ILK downstream signaling targets p-Akt and p-GSK3beta in T24 cells. We further find that bladder cancer with a high-metastasis capability shows higher vimentin, Snail, Slug and Twist and lower E-cadherin and RI expression in human clinical specimens. Finally, we provide evidence that the up-regulation of RI inhibits tumorigenesis and metastasis of bladder cancer in vivo. Thus, RI might play a novel role in the development of bladder cancer through regulating EMT and the ILK signaling pathway.

[482]

**TÍTULO / TITLE:** - Signet Ring Cell Colorectal Carcinoma: A Distinct Subset of Mucin-poor Microsatellite-stable Signet Ring Cell Carcinoma Associated With Dismal Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Surg Pathol. 2013 May 15.

●●Enlace al texto completo (gratis o de pago)

[1097/PAS.0b013e3182851e2b](#)

**AUTORES / AUTHORS:** - Hartman DJ; Nikiforova MN; Chang DT; Chu E; Bahary N; Brand RE; Zureikat AH; Zeh HJ; Choudry H; Pai RK

**INSTITUCIÓN / INSTITUTION:** - Departments of \*Pathology parallelSurgical Oncology double daggerInternal Medicine, Division of Medical Oncology section signDepartment of Internal Medicine, Division of Gastroenterology, University of Pittsburgh Medical Center, Pittsburgh, PA daggerDepartment of Radiation Oncology, Stanford University, Stanford, CA.

**RESUMEN / SUMMARY:** - We evaluated a consecutive series of signet ring cell colorectal carcinomas in an attempt to correlate the histopathologic pattern of infiltration with molecular alterations and prognosis. Of the 4760 primary colorectal carcinomas surgically resected between the years 2002 and 2012, 53 (1%) were composed of >50% signet ring cells. Of the 53 signet ring cell carcinomas, 40 (75%) were composed of >50% extracellular mucin with signet ring cells floating within pools of mucin and were subclassified as mucin-rich signet ring cell carcinomas. Thirteen (25%) carcinomas were characterized by diffusely infiltrating carcinomas with minimal to no extracellular mucin and were subclassified as mucin-poor signet ring cell carcinomas. All 13 mucin-poor signet ring cell carcinomas were either stage III or IV, whereas many cases of mucin-rich signet ring cell carcinoma were stage I or II (17 cases) (P=0.005). Compared with mucin-rich tumors, mucin-poor signet ring cell carcinomas more frequently demonstrated adverse histologic features such as lymphatic invasion (13/13, 100% vs. 22/40, 55%; P=0.002), venous invasion (6/13, 46% vs. 3/40, 8%; P=0.004), and perineural invasion (11/13, 85% vs. 9/40, 23%; P=0.0001). Twenty-three of 53 (43%) signet ring cell carcinomas demonstrated high levels of microsatellite instability (MSI-H). Twenty-two of 23 (96%) MSI-H signet ring cell carcinomas were mucin rich; only 1 MSI-H signet ring carcinoma was mucin poor (P=0.0033). Mucin-poor signet ring cell carcinoma had significantly reduced overall and recurrence-free survival compared with mucin-rich signet ring cell carcinomas (P=0.0035 and 0.0001, respectively), even when adjusting for tumor stage. Mucin-poor signet ring cell carcinoma had a higher propensity for peritoneal dissemination (5/13, 38%) compared with mucin-rich signet ring cell carcinoma (5/40, 12.5%), although this was not statistically significant (P=0.052). Finally, MSI-H and microsatellite-stable signet ring cell carcinomas had similar overall and recurrence-free survival (P=0.2266 and 0.1055, respectively), even when adjusting for tumor stage. In conclusion, we identified a unique subset of signet ring cell colorectal carcinoma with diffuse infiltration

and minimal to no extracellular mucin (mucin-poor signet ring cell carcinoma), which lacks MSI-H and has a dismal prognosis with an aggressive clinical course often with peritoneal dissemination. Further, our results confirm that MSI does not affect survival in colorectal signet ring cell carcinomas.

[483]

**TÍTULO / TITLE:** - kappa-Opioid receptor in the nucleus is a novel prognostic factor of esophageal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Pathol. 2013 Apr 8. pii: S0046-8177(13)00064-6. doi: 10.1016/j.humpath.2012.11.025.

●●Enlace al texto completo (gratis o de pago)

[1016/j.humpath.2012.11.025](#)

**AUTORES / AUTHORS:** - Zhang YF; Xu QX; Liao LD; Xu XE; Wu JY; Shen J; Wu ZY; Shen JH; Li EM; Xu LY

**INSTITUCIÓN / INSTITUTION:** - Institute of Oncologic Pathology, Medical College of Shantou University, Shantou 515041, PR China.

**RESUMEN / SUMMARY:** - Opioid receptors, members of the G-protein-coupled receptor superfamily, appear to be involved in cancer progression. However, the expression and significance of opioid receptors in esophageal squamous cell carcinoma (ESCC) remain unclear. In this study, we demonstrated by flow cytometry that mu, delta, and kappa-opioid receptors (MOR, DOR, and KOR) are expressed to various degrees in ESCC cell lines. The KOR protein was further examined by several methods in ESCC cell lines and tissues. Immunocytochemical staining localized KOR to the cell membrane in KYSE180 cells and the nucleus in EC109 cells, whereas no signal or weak staining of the cytoplasm was observed in KYSE150 cells. The expression of KOR was confirmed in ESCC cells by Western blotting. Furthermore, immunohistochemistry staining showed that KOR was up-regulated in ESCC tissues compared with nontumorous esophageal epithelium (P = .004, chi2 test). Moreover, high nuclear KOR expression was significantly correlated with lymph node metastasis in 256 ESCC cases (R = 0.144; P = .030, Kendall tauB test). Patients with high nuclear KOR expression in ESCC had a significantly poorer prognosis (P = .001, log-rank test). Multivariate Cox analysis revealed that KOR in the nucleus was an independent prognostic factor (hazard ratio, 1.789; 95% confidence interval, 1.177-2.720; P = .006). Our results suggest that KOR is involved in the carcinogenesis or progression of ESCC and that nuclear KOR may be indicative of prognosis.

[484]

**TÍTULO / TITLE:** - Calycosin Induces Apoptosis by Upregulation of RASD1 in Human Breast Cancer Cells MCF-7.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Horm Metab Res. 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1055/s-0033-1341510](#)

**AUTORES / AUTHORS:** - Tian J; Duan YX; Bei CY; Chen J

**INSTITUCIÓN / INSTITUTION:** - Department of physiology, Guilin Medical University, Guilin, China.

**RESUMEN / SUMMARY:** - Breast cancer is a leading cause of cancer death among women, and the failure of normal apoptosis has been proved in the development of breast cancer. The phytoestrogen, calycosin, is extracted from Chinese medical herb Radix astragali. We recently reported that calycosin successfully stimulated proliferation of ER-positive MCF-7 human breast cancer cells at low concentration. In the present study, we assessed the proapoptotic function of calycosin in MCF-7 cells at high concentration in vitro, as well as the possible mechanism of its effect. MCF-7 cells were treated with different concentrations of calycosin, and then detected by MTT assay for cellular viability, Hoechst assay, and flow cytometry for apoptosis. RASD1 is identified as a Ras-family member and a regulator in MAPK-mediated cascade leading to cell proliferation or apoptosis. To provide insight into the functions of RASD1 signaling pathway in calycosin-induced apoptosis, the expression of Bcl-2, Bax, and RASD1 in calycosin-treated cells were determined by Western blot assay. The results showed that high concentrations of calycosin significantly suppressed the proliferation of MCF-7 cells and promoted cell apoptosis. Moreover, compared with control group, the expression of Bcl-2 decreased with calycosin in MCF-7 cells, while Bax increased, which was significantly correlated with elevated expression of RASD1. Together, we present evidence that at relatively high concentration calycosin triggered cell apoptosis through the mitochondrial apoptotic pathway by upregulating RASD1. And for the first time, this study revealed that calycosin may have potential as a therapeutic agent for the treatment of breast cancer.

[485]

**TÍTULO / TITLE:** - Unresectable Colorectal Liver Metastases: The Safety and Efficacy of Conversion Therapy Using Hepatic Arterial Infusion Immunochemotherapy with 5-Fluorouracil and Polyethylene Glycol-Interferon alpha-2a.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg. 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1007/s00268-013-2043-](#)

[4](#)

**AUTORES / AUTHORS:** - Nakai T; Okuno K; Kitaguchi H; Ishikawa H; Yamasaki M

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Faculty of Medicine, Kinki University, 377-2 Ohno-Higashi, Osaka-Sayama, 589-8511, Osaka, Japan, [nakai@surg.med.kindai.ac.jp](mailto:nakai@surg.med.kindai.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: Hepatic arterial infusion (HAI) or systemic chemotherapy has been used to treat unresectable colorectal liver metastases. The prognosis of the disease in recent years has been improved because chemotherapy is performed before hepatectomy to reduce tumor size (conversion therapy). The purpose of this study was to investigate the safety and efficacy of conversion therapy following HAI immunochemotherapy. METHODS: Hepatic arterial infusion of 5-fluorouracil (5-FU)/polyethylene glycol (PEG)-IFNalpha-2a was performed in 21 patients. The primary endpoint was the safety of HAI and hepatectomy. The secondary endpoints were response rate, rate of conversion to hepatectomy, survival rate, and prognostic factors. RESULTS: With regard to side effects, drugs were discontinued temporarily in one patient because of a decrease in white blood cell count; however, other patients continued chemotherapy. The response rate with HAI was 61.9 %, and the conversion rate was 38.1 %. Hepatectomy was completed successfully without mortality. Median progression-free survival (PFS) was 11.5 months (with and without conversion, 16.7 and 4.8 months, respectively;  $p = 0.021$ ). Median overall survival was 34.6 months (with and without conversion, 48.4 and 26.6 months, respectively;  $p = 0.003$ ). Prognosis was poor when the number of metastatic tumors was  $\geq 10$  [PFS: hazard ratio (HR) 32.21,  $p = 0.003$ ; overall survival (OS): HR 9.13,  $p = 0.07$ ], but prognosis improved after hepatectomy (OS: HR 0.08,  $p = 0.09$ ). CONCLUSIONS: Hepatic arterial infusion immunochemotherapy with 5-FU/PEG-IFNalpha-2a was performed safely without major side effects. Prognosis is expected to improve after successful conversion to hepatectomy.

[486]

**TÍTULO / TITLE:** - Quercetin synergizes with 2-methoxyestradiol inhibiting cell growth and inducing apoptosis in human prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):357-63. doi: 10.3892/or.2013.2469. Epub 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2469](#)

**AUTORES / AUTHORS:** - Wang G; Song L; Wang H; Xing N

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, P.R. China.

**RESUMEN / SUMMARY:** - Lack of effective treatment options for castration-resistant prostate cancer reinforces the great need to develop novel drug therapies. Quercetin is a plant-derived flavonoid that can induce apoptosis in prostate cancer cells. 2-Methoxyestradiol (2-ME) is an endogenous estrogenic metabolite that also has antineoplastic activity. However, these two agents have limited bioavailability. Herein, we explored the antiproliferative and proapoptotic activities of quercetin combined with 2-ME in both androgen-dependent LNCaP and androgen-independent PC-3 human prostate cancer cell lines. Compared

to quercetin and 2-ME alone, combining quercetin with 2-ME at appropriate concentrations i) showed synergistic antiproliferative and proapoptotic activities; ii) increased G2/M phase population of cells; iii) decreased the ratio of Bcl-2/Bax significantly. The combination of quercetin and 2-ME is a new clinically relevant treatment regimen which has the potential of enhancing the antitumor effect on prostate cancer and lessening the side effect of either quercetin or 2-ME alone.

[487]

**TÍTULO / TITLE:** - Active extracts of black tea (*Camellia Sinensis*) induce apoptosis of PC-3 prostate cancer cells via mitochondrial dysfunction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 May 28. doi: 10.3892/or.2013.2504.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2504](#)

**AUTORES / AUTHORS:** - Sun S; Pan S; Miao A; Ling C; Pang S; Tang J; Chen D; Zhao C

**INSTITUCIÓN / INSTITUTION:** - Drink Plant Research Institute/Tea Research Center, Guangdong Academy of Agricultural Sciences, Guangzhou, Guangdong 510640, P.R. China.

**RESUMEN / SUMMARY:** - Cancer of the prostate gland is the most common invasive malignancy and the second leading cause of cancer-related death in human males. Many studies have shown that black tea reduces the risk of several types of cancer. We studied the effects of active extracts of black tea and the black tea polyphenols theaflavins (TFs), on the cellular proliferation and mitochondria of the human prostate cancer cell line PC-3. Our studies revealed that Yinghong black tea extracts (YBT), Assam black tea extracts (ABT) and TFs inhibited cell proliferation in a dose-dependent manner. We also showed that TFs, YBT and ABT affected the morphology of PC-3 cells and induced apoptosis or even necrosis in PC-3 cells. In addition, it was observed that the samples significantly caused loss of the mitochondrial membrane potential, release of cytochrome c from the intermembrane space into the cytosol, decrease of the ATP content and activation of caspase-3 compared with the control. Taken together, these findings suggest that black tea could act as an effective anti-proliferative agent in PC-3 cells, and TFs, YBT and ABT induced apoptosis of PC-3 cells through mitochondrial dysfunction.

[488]

**TÍTULO / TITLE:** - NK4 regulates 5-fluorouracil sensitivity in cholangiocarcinoma cells by modulating the intrinsic apoptosis pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):448-54. doi: 10.3892/or.2013.2427. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2427](https://doi.org/10.3892/or.2013.2427)

**AUTORES / AUTHORS:** - Ge X; Wang Y; Li Q; Yu H; Ji G; Miao L

**INSTITUCIÓN / INSTITUTION:** - Institute of Digestive Endoscopy and Medical Center for Digestive Diseases, Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210011, P.R. China.

**RESUMEN / SUMMARY:** - The aim of the present study was to investigate the role of NK4, an antagonist for hepatocyte growth factor (HGF) and the Met receptor, in regulating the response of cholangiocarcinoma (CCA) cells to 5-fluorouracil (5-FU). We established the CCA cell line, HuCC-T1, to produce abundant NK4 (Hu-NK4). Cell proliferation, cell cycle distribution, apoptosis, 5-FU metabolism and intracellular signaling were examined. There were no significant differences in the mRNA levels of thymidylate synthase, thymidine phosphorylase and dihydropyrimidine dehydrogenase between the mock-transfected control Hu-Em cells and Hu-NK4 cells, suggesting that NK4 expression does not alter 5-FU metabolism. Moreover, cell cycle analysis showed that 5-FU treatment caused a decrease in the proportion of cells in the G2/M phase while NK4 gene expression had little effect on the cell cycle distribution. However, 5-FU-induced apoptosis was significantly increased in the Hu-NK4 cells when compared to that in the Hu-Em cells. Further investigation revealed that NK4 gene expression enhanced 5-FU-induced caspase-3 and caspase-9 activation, and that the apoptosis of cells was associated with modulation of expression of the Bcl-2 family members. Furthermore, western blot analysis revealed that both NK4 and 5-FU were inhibitors for HGF-induced phosphorylation of Met, but they may be independent factors. Collectively, these results suggest that following 5-FU treatment in CCA cell lines, NK4 was involved in apoptosis induction through the intrinsic mitochondrial pathway. This indicates that NK4 may be an important mediator of 5-FU-induced cell death. Moreover, downregulation of NK4 in response to 5-FU may represent an intrinsic mechanism of resistance to this anticancer drug.

[489]

**TÍTULO / TITLE:** - Ent-11alpha-hydroxy-15-oxo-kaur-16-en-19-oic-acid induces apoptosis and cell cycle arrest in CNE-2Z nasopharyngeal carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jun;29(6):2101-8. doi: 10.3892/or.2013.2375. Epub 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2375](https://doi.org/10.3892/or.2013.2375)

**AUTORES / AUTHORS:** - Wu K; Liu Y; Lv Y; Cui L; Li W; Chen J; Liang NC; Li L

**INSTITUCIÓN / INSTITUTION:** - Guangdong Key Laboratory for Research and Development of Natural Drugs, Guangdong Medical College, and Department of General Surgery, 422 Hospital of PLA, Zhanjiang, Guangdong 524023, PR China.

**RESUMEN / SUMMARY:** - Ent-11alpha-hydroxy-15-oxo-kaur-16-en-19-oic-acid (5F), a compound isolated from *Pteris semipinnata* L. (PsL), inhibits cell proliferation and induces cell apoptosis in several cancer lines. We found that 5F induced apoptosis and G2 phase cell cycle arrest in the CNE-2Z nasopharyngeal carcinoma (NPC) cells, accompanied by a decrease of NF-kappaB expression. 5F suppressed the viability of CNE-2Z cells in a time- and dose-dependent manner. 5F induced G2/M phase cell cycle arrest, but did not induce p21. Further analysis revealed that CNE-2Z cells harbored two p53 mutations. 5F treatment resulted in mitochondrial apoptosis, associated with increased Bax/Bcl-2 ratio, upregulation of cytochrome c in the cytosol, decreased NF-kappaB-p65 and increased IkappaB. Of note, 5F significantly sensitized CNE-2Z cells to cisplatin. 5F did not increase ROS, but reduced ROS production alone or in combination with cisplatin. Our data suggest that 5F is a potential anti-NPC drug for the development of single agent therapy and therapy in combination with cisplatin.

[490]

**TÍTULO / TITLE:** - Comparison of EGFR-TKI and chemotherapy in the first-line treatment of advanced EGFR mutation-positive NSCLC.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neoplasma. 2013;60(4):425-31. doi: 10.4149/neo\_2013\_055.

●●Enlace al texto completo (gratis o de pago) [4149/neo\\_2013\\_055](#)

**AUTORES / AUTHORS:** - Fiala O; Pesek M; Finek J; Benesova L; Bortlicek Z; Minarik M

**RESUMEN / SUMMARY:** - Molecular targeted therapy based on EGFR tyrosine kinase inhibitors (EGFR-TKI) is currently a state of the art option for management of advanced stage NSCLC. Activating EGFR mutations are preferable for a good treatment response to EGFR-TKI. The presented retrospective study evaluated a clinical observation of EGFR-TKI aiming at its efficacy and safety in comparison to a standard chemotherapy in the first-line treatment of advanced stage NSCLC. Total number of patients with advanced stage (IIIB, IV) EGFR mutation-positive NSCLC was 54 of which 23 were treated with EGFR-TKI and 31 patients with various chemotherapy regimens in the first line. The treatment efficacy was characterized in terms of disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). The comparison of DCR was performed using Fisher's exact test and the differences in survival were tested using log-rank test. DCR for EGFR-TKI treatment was 95.6% vs. 70.9% for chemotherapy (p=0.032). Median of PFS in patients treated with EGFR-TKI was 7.2 months vs. 2.5 months in patients treated with chemotherapy (p<0.001). Median of OS was 14.5 months vs. 21.4 months (p=0.729). EGFR-TKI was associated with higher incidence of skin rash and diarrhoea; chemotherapy was associated with higher incidence of

haematologic adverse events and nausea or vomiting. The analysis results showed a favourable DCR and PFS in patients treated with EGFR-TKI in the first line. The non-significant difference in OS could be attributed to cross-over during the patient follow-up as well as the differences in performance status and age between both groups. EGFR-TKI is the optimal choice for the first-line treatment of EGFR mutation-positive NSCLC. Keywords: EGFR-TKI, first-line treatment, NSCLC, erlotinib, gefitinib, targeted treatment of NSCLC.

[491]

**TÍTULO / TITLE:** - Biological rationale and clinical use of interferon in the classical BCR-ABL-negative myeloproliferative neoplasms.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Interferon Cytokine Res. 2013 Apr;33(4):145-53. doi: 10.1089/jir.2012.0120.

●●Enlace al texto completo (gratis o de pago) [1089/jir.2012.0120](http://1089/jir.2012.0120)

**AUTORES / AUTHORS:** - Stein BL; Tiu RV

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**RESUMEN / SUMMARY:** - Because of its antiapoptotic, antiproliferative, and immunomodulatory properties, interferon (IFN) has been broadly used as an antiviral and antineoplastic agent. These properties are particularly suitable for the treatment of the classical BCR-ABL-negative myeloproliferative neoplasms (MPN), including essential thrombocytosis (ET), polycythemia vera (PV), and myelofibrosis (MF). In the MPN, IFN has been shown to suppress megakaryopoiesis, inhibit erythroid colony-forming cells, suppress bone marrow fibroblast progenitors, induce cytogenetic remission, and reduce the JAK2 V617F allele burden, sometimes completely. Although efficacy has long been demonstrated in the MPN, toxicities were frequent with recombinant IFN, tempering enthusiasm. However, with pegylated-IFN, because of less toxicity, there has been renewed interest, and recent studies in the MPN have shown hematologic and molecular response or remission in ET and PV; a smaller study in early MF has shown IFN's potential to retard fibrosis. The role of IFN in the treatment of MPN is being re-evaluated on the basis of these studies, and will be better defined as results return from an ongoing international study.

[492]

**TÍTULO / TITLE:** - Pancreatic secretory trypsin inhibitor causes autocrine-mediated migration & invasion in bladder cancer & phosphorylates the EGF receptor, Akt 2 & 3, ERK1 & 2.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Physiol Renal Physiol. 2013 May 22.

- Enlace al texto completo (gratis o de pago)

[1152/ajprenal.00357.2012](http://1152/ajprenal.00357.2012)

**AUTORES / AUTHORS:** - Marchbank T; Mahmood A; Playford RJ

**INSTITUCIÓN / INSTITUTION:** - 1Institute of Cell and Molecular Science, Barts & The London School of Medicine, Queen Mary, University of London.

**RESUMEN / SUMMARY:** - Pancreatic secretory trypsin inhibitor is expressed in most bladder carcinomas where its pathophysiological relevance is unclear. Using recombinant normal sequence PSTI/TATI, a variant associated with familial pancreatitis (N34S), an active site inactivated variant (R18/V19) and immunoneutralization and RNA interference-mediated knockdown (KD) techniques, we investigated the actions of PSTI/TATI on cell migration (wounding monolayers), collagen invasion (gel invasion assays) and proliferation (Alamar blue) on 253J, RT4 and HT1376 human bladder carcinoma cell lines. All three forms of PSTI/TATI stimulated migration two-fold and normal sequence PSTI/TATI showed synergistic promigratory effects when added with EGF. Addition of structurally unrelated soya bean trypsin inhibitor had no pro-migratory activity. Similar results were seen using collagen invasion assays although the active site mutated variant had no pro-invasive activity, probably due to reduced Akt2 activation. PSTI/TATI did not stimulate proliferation despite acting, at least partially, through the EGF receptor as effects of PSTI/TATI were truncated by adding an EGFR blocking antibody or the tyrosine kinase inhibitor Tyrphostin. Cell lines produced endogenous PSTI/TATI and PSTI/TATI RNA interference knockdown or addition of PSTI/TATI, EGF-receptor or Tyrphostin blocking agents reduced migration and invasion below baseline. PSTI/TATI induced phosphorylation of the EGF receptor, ERK1 and 2, Akt2 and 3, JNK1, MKK3 and RSK1. This profile was more limited than that induced by EGF and did not include Akt1, probably explaining lack of pro-proliferative activity. Our findings of autocrine stimulation and synergistic responses between EGF & PSTI/TATI at concentrations found in urine and tissue suggest PSTI/TATI has pathophysiological relevance.

[493]

**TÍTULO / TITLE:** - Autophagy induced by silibinin protects human epidermoid carcinoma A431 cells from UVB-induced apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Photochem Photobiol B. 2013 Jun 5;123:23-31. doi: 10.1016/j.jphotobiol.2013.03.014. Epub 2013 Apr 6.

- Enlace al texto completo (gratis o de pago)

[1016/j.jphotobiol.2013.03.014](http://1016/j.jphotobiol.2013.03.014)

**AUTORES / AUTHORS:** - Liu W; Otkur W; Li L; Wang Q; He H; Ye Y; Zhang Y; Hayashi T; Tashiro S; Onodera S; Ikejima T

**INSTITUCIÓN / INSTITUTION:** - China-Japan Research Institute of Medical and Pharmaceutical Sciences, Shenyang Pharmaceutical University, Shenyang 110016, China.

**RESUMEN / SUMMARY:** - Ultraviolet B (UVB) in the sun light is a major cause of skin damage, which accompanies complex alterations in irradiated skin cells, including DNA lesions, oxidative stress, inflammation and caspase activation. The protection against UVB damage requires multiple interruptions such as repair of the DNA lesions, scavenging of the reactive oxygen species (ROS), repression of the inflammation and others. Silibinin is suggested as an anti-UVB reagent, but the underlying mechanisms have not been fully elucidated. In this study, we found a role of autophagy in the anti-UVB effect of silibinin in A431 cells. Autophagy was reduced after UVB-irradiation while restored by silibinin through the suppression of the IGF-1R signalling pathway. The protective effect of silibinin in UVB-irradiated A431 cells was further enhanced by pre-treatment with an autophagy inducer, rapamycin, while it was reversed by an autophagy inhibitor, wortmannin, indicating that elevated autophagy contributed to the cell survival. Consistently, cell apoptosis was augmented by siRNAs targeting Beclin 1 and Atg5, supporting the hypothesis that autophagy induced by silibinin plays a protective role against UVB-induced epidermal apoptosis.

[494]

**TÍTULO / TITLE:** - Resveratrol has anti-leukemic activity associated with decreased O-GlcNacylated proteins.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Hematol. 2013 Apr 15. pii: S0301-472X(13)00157-4. doi: 10.1016/j.exphem.2013.04.004.

●●Enlace al texto completo (gratis o de pago)

[1016/j.exphem.2013.04.004](#)

**AUTORES / AUTHORS:** - Tomic J; McCaw L; Li Y; Hough MR; Ben-David Y; Moffat J; Spaner DE

**INSTITUCIÓN / INSTITUTION:** - Division of Molecular and Cellular Biology, Sunnybrook Research Institute, Toronto, Canada; Department of Medical Biophysics, University of Toronto, Toronto, Canada; Department of Molecular Genetics, Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada.

**RESUMEN / SUMMARY:** - CLL cells are characterized by high levels of proteins that are post-translationally modified by O-linked beta-N-acetylglucosamine (O-GlcNAc) moieties, but it is not clear whether O-GlcNAc is a relevant therapeutic target. The nutraceutical resveratrol is cytotoxic to chronic lymphocytic leukemia cells in vitro. In this study, we found that resveratrol has therapeutic activity as a single agent in vivo in both human chronic lymphocytic leukemia patients and mice with erythroleukemia. Blood and splenic O-GlcNAc levels reflected the changes in tumor burden. Resveratrol directly lowered O-GlcNAc

levels in leukemia cells through proteasomal activation, but increasing O-GlcNAc levels in vitro did not prevent cell death. These findings suggest that resveratrol has potential as a novel treatment for some forms of chronic and acute leukemia, and the measurement of O-GlcNAc levels could be a surrogate marker for therapeutic responses.

[495]

**TÍTULO / TITLE:** - Predictive value of serum human epididymis protein 4 and cancer antigen 125 concentrations in endometrial carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Obstet Gynecol. 2013 Apr 10. pii: S0002-9378(13)00363-3. doi: 10.1016/j.ajog.2013.04.014.

●●Enlace al texto completo (gratis o de pago) [1016/j.ajog.2013.04.014](http://1016/j.ajog.2013.04.014)

**AUTORES / AUTHORS:** - Saarelainen SK; Peltonen N; Lehtimäki T; Perheentupa A; Vuontisjärvi MH; Maenpää JU

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland. Electronic address: [sami.saarelainen@uta.fi](mailto:sami.saarelainen@uta.fi).

**RESUMEN / SUMMARY:** - **OBJECTIVE:** The purpose of this study was to evaluate the performance of preoperative serum levels of human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) in the prediction of the presence of metastases in endometrial carcinoma. **STUDY DESIGN:** Preoperative sera were collected from 98 women with a diagnosis of endometrial carcinoma. The concentrations of HE4 and CA125 were assessed by enzyme-linked immunosorbent assay and correlated with the results of the final histopathologic report. **RESULTS:** Fourteen patients had metastases ( $\geq$ stage IIIA, International Federation of Gynecology and Obstetrics 2009 classification). The serum concentrations of HE4 and CA125 were higher in the group with metastases than in the group without metastases (median [interquartile range], 148.6 pmol/L [71.6-219.1 pmol/L] vs 77.2 pmol/L [52.9-99.3 pmol/L];  $P = .001$ ; and 20.0 U/mL [10.1-70.8 U/mL] vs 4.3 U/mL [2.9-10.4 U/mL];  $P < .001$ , respectively). By a multivariate analysis, the combination of HE4 and CA125 (a risk score algorithm) was the only predictive factor for the presence of metastases (odds ratio, 21.562; 95% confidence interval, 5.472-84.963;  $P < .001$ ), and the grade was the predictor for a deep ( $\geq 50\%$ ) myometrial invasion by the tumor (odds ratio, 2.005; 95% confidence interval, 1.123-3.581;  $P = .019$ ). The sensitivity, specificity, positive predictive value, and negative predictive value for the combination of the markers to predict the presence of metastases were 71.4%, 89.5%, 55.6%, and 94.4%, respectively. **CONCLUSION:** A combination of preoperative HE4 and CA125 seems to be a better predictor of metastatic disease than either 1 alone in endometrial carcinoma.

[496]

**TÍTULO / TITLE:** - Factors predicting trastuzumab-related cardiotoxicity in a real-world population of women with HER2+ breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1717-20.

**AUTORES / AUTHORS:** - Naumann D; Rusius V; Margiotta C; Nevill A; Carmichael A; Rea D; Sintler M

**INSTITUCIÓN / INSTITUTION:** - Sandwell and West Birmingham Hospitals NHS Trust, Lyndon, West Bromwich, West Midlands, UK. [david.naumann@nhs.net](mailto:david.naumann@nhs.net)

**RESUMEN / SUMMARY:** - BACKGROUND: Trastuzumab may improve disease-free survival after chemotherapy for HER2-positive breast cancer. However, it carries a risk of cardiotoxicity and counseling patients about such risks is part of informed consent. The National Institute for Health and Clinical Excellence has published guidelines for cardiac assessment before and during treatment with trastuzumab in order to minimize the risk of cardiotoxicity. The aim of the present study was to identify risk factors for cardiotoxicity attributed to trastuzumab in a cohort population treated for primary and metastatic breast cancer. PATIENTS AND METHODS: This study included all women who started a course of trastuzumab from February 2006 - February 2011 at three NHS Trusts in the UK. Their cardiac function during treatment was recorded and cardiotoxicity was defined as a decrease in left ventricular ejection fraction (LVEF)  $\geq 10\%$  and a reduction to  $<50\%$ , or a clinical reduction in cardiac function as defined by the New York Heart Association. An independent samples t-test was used to assess whether patient age predicted cardiotoxicity. Pearson's chi-squared tests of independence were used to investigate the association between cardiotoxicity, the indication for trastuzumab, exposure to anthracycline chemotherapy, and Adult Comorbidity Evaluation-27 index (ACE-27) scores. RESULTS: There were 388 female patients included in this study, with a mean age of 54 (range = 25-100 years). Cardiotoxicity was recorded during 61 (15.72%) courses of trastuzumab treatment. There were no associations between cardiotoxicity and the three factors (indication, exposure to anthracyclines, or ACE-27 score), and no significant difference in age between patients with and those without cardiotoxicity. However, subgroup analysis of patients who experienced cardiotoxicity (n = 61) showed that there was a negative correlation (-0.455; p = 0.001) between time-to-first cardiotoxicity event and age in the group who had received concurrent anthracycline therapy (n=49). CONCLUSION: In a real-world 5-year population of patients who received trastuzumab, the incidence of drug-related cardiotoxicity was higher than expected, and the age of the patients appeared to predict the first cardiotoxic event amongst those who experienced cardiotoxicity and had received prior anthracyclines. However, incidence of cardiotoxicity in the whole cohort did not appear to be predicted by age, comorbidity, indication, or exposure to anthracyclines. Vigilance, therefore,

seems justified when conducting cardiac surveillance for all patients during treatment with trastuzumab, but especially for those who are elderly and receiving concurrent anthracycline therapy.

[497]

**TÍTULO / TITLE:** - S100 calcium-binding protein A4 is a novel independent prognostic factor for the poor prognosis of gastric carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):111-8. doi: 10.3892/or.2013.2419. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2419](#)

**AUTORES / AUTHORS:** - Zhao Y; Zhang T; Wang Q

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, P.R. China.

**RESUMEN / SUMMARY:** - Overexpression of the S100 calcium-binding protein A4 (S100A4) is involved in epithelial-to-mesenchymal transition, oncogenic transformation, angiogenesis, cytoskeletal integrity and cancer metastasis. Here, we elucidated the role of S100A4 in tumorigenesis and progression of gastric carcinomas. S100A4 expression in gastric carcinomas, adenomas and adjacent non-neoplastic mucosa was analyzed by immunohistochemical, real-time reverse transcriptase (RT)-polymerase chain reaction (PCR) and western blot analyses, and was correlated with various clinicopathological parameters. S100A4 protein expression was increased gradually in the following order: gastritis (19.2%), intestinal metaplasia (IM; 23.3%), dysplasia (34.9%) and carcinoma (55.2%;  $P < 0.001$ ). S100A4 was positively correlated with tumor size, depth of invasion, lymphatic invasion, lymph node metastasis and tumor-node-metastasis (TNM) staging ( $P < 0.05$ ), but not with the age and gender of the carcinoma patients ( $P > 0.05$ ). Intestinal-type (IT) carcinomas showed a higher S100A4 expression than diffuse-type (DT) carcinomas ( $P < 0.001$ ). S100A4 mRNA expression also increased in the following order: gastritis  $<$  IM  $<$  dysplasia  $<$  carcinoma ( $P < 0.05$ ). S100A4 overexpression was observed in gastric carcinomas with a larger diameter, deeper invasion, lymph node metastasis and in IT carcinoma ( $P < 0.05$ ). Univariate analysis using the Kaplan-Meier method indicated a lower cumulative survival rate for patients with weak or moderate S100A4 expression compared with patients not expressing S100A4 ( $P < 0.001$ ). Multivariate analysis using Cox's proportional hazard model demonstrated that depth of invasion, lymphatic or venous invasion, lymph node metastasis, TNM staging and S100A4 expression were independent factors for poor patient prognosis ( $P < 0.05$ ). In conclusion, S100A4 upregulation is positively associated with the pathogenesis, growth, invasion, metastasis and differentiation of gastric carcinomas. S100A4 may be a promising marker indicative of the aggressive behavior and prognosis of gastric carcinomas.

[498]

**TÍTULO / TITLE:** - OSU-03012, a non-cox inhibiting celecoxib derivative, induces apoptosis of human esophageal carcinoma cells through a p53/Bax/cytochrome c/caspase-9-dependent pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 May 6.

●●Enlace al texto completo (gratis o de pago)

[1097/CAD.0b013e328362469f](#)

**AUTORES / AUTHORS:** - Liu J; Qin CK; Lv W; Zhao Q; Qin CY

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Gastroenterology bDepartment of Surgery, Provincial Hospital Affiliated to Shandong University, Jinan, China.

**RESUMEN / SUMMARY:** - OSU-03012 is a celecoxib derivative devoid of cyclooxygenase-2 inhibitory activity. It was previously reported to inhibit the growth of some tumor cells through the AKT-signaling pathway. In the current study, we assessed the ability of OSU-03012 to induce apoptosis in human esophageal carcinoma cells and the mechanism by which this occurs. A cell proliferation assay indicated that OSU-03012 inhibited the growth of human esophageal carcinoma cell lines with an IC<sub>50</sub> below 2 μmol/l and had the most effective cytotoxicity against Eca-109 cells. Terminal deoxynucleotidyl transferase-mediated nick-end labeling assay and flow cytometry analysis showed that OSU-03012 could induce the apoptosis in Eca-109 cells. After treatment of Eca-109 cells with 2 μmol/l OSU-03012 for 24 h, the apoptosis index increased from 14.07 to 53.72%. OSU-03012 treatment resulted in a 30-40% decrease in the mitochondrial membrane potential and caused cytochrome c release into the cytosol. Further studies with caspase-9-specific and caspase-8-specific inhibitors (z-LEHDfmk and z-IETDfmk, respectively) pointed toward the involvement of the caspase-9 pathway, but not the caspase-8 pathway, in the execution of OSU-03012-induced apoptosis. Immunoblot analysis demonstrated that OSU-03012-induced cellular apoptosis was associated with upregulation of Bax, cleaved caspase-3, and cleaved caspase-9. Ser-15 of p53 was phosphorylated after 24 h of treatment of the cancer cells with OSU-03012. This increase in p53 was associated with the decrease in Bcl-2 and increase in Bax. An inhibitor of p53, pifithrin-α, attenuated the anticancer effects of OSU-03012 and downregulated the expression of Bax and cleaved caspase-9. Altogether, our results show that OSU-03012 could induce apoptosis in human esophageal carcinoma cells through a p53/Bax/cytochrome c/caspase-9-dependent pathway.

[499]

**TÍTULO / TITLE:** - Granulocyte colony-stimulating factor as secondary prophylaxis of febrile neutropenia in the management of advanced-stage

Hodgkin lymphoma treated with adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy: a decision analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 29.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.796046](#)

**AUTORES / AUTHORS:** - Graczyk J; Cheung MC; Buckstein R; Chan K

**INSTITUCIÓN / INSTITUTION:** - Odette Cancer Centre, Sunnybrook Health Sciences Centre, Division of Hematology/Oncology, Toronto, Canada.

**RESUMEN / SUMMARY:** - Current practice guidelines are unclear regarding the role of secondary prophylaxis of febrile neutropenia in advanced-stage Hodgkin lymphoma despite several small retrospective studies that demonstrate the omission of growth factors to be a safe and economic practice. We used a decision-analytic model to compare secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) to no G-CSF with the onset of severe neutropenia for a hypothetical cohort of patients with advanced-stage Hodgkin lymphoma treated with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). There was a net benefit of 0.017 years and 0.037 quality-adjusted life years for no G-CSF use in severe neutropenia. On microsimulation (10 000 trials), 96% of the simulations showed that the no G-CSF strategy is preferred to the use of G-CSF. This finding was robust across a wide range of sensitivity analyses. Our analysis suggests that G-CSF not be used as secondary prophylaxis of febrile neutropenia in advanced-stage Hodgkin lymphoma.

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[500]

**TÍTULO / TITLE:** - Toll-like receptor 3 expression inhibits cell invasion and migration and predicts a favorable prognosis in neuroblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Mar 27. pii: S0304-3835(13)00252-8. doi: 10.1016/j.canlet.2013.03.024.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.03.024](#)

**AUTORES / AUTHORS:** - Hsu WM; Huang CC; Wu PY; Lee H; Huang MC; Tai MH; Chuang JH

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - To evaluate the clinical significance of TLR3 expression on neuroblastomas, we performed immunohistochemical study on archival tissues and in vitro studies on neuroblastoma cell lines. The results showed that positive TLR3 expression was associated with favorable histology and prognosis. Activation of TLR3 by polyinosinic:polycytidylic acid [poly(I:C)] treatment is effective to suppress cell migration and invasion and to decrease organized assembly of F-actin and filopodia formation, in TLR3-expressing SK-

N-AS cells, which could be reversed by TLR3-targeting siRNA treatment. TLR3 agonist poly(I:C) promotes GAP-43 expression also in SK-N-AS cells only. Taken together, TLR3 could serve to predict favorable behavior in neuroblastomas.

[501]

**TÍTULO / TITLE:** - Antiproliferative and Apoptosis-inducing Activity of Curcumin against Human Gallbladder Adenocarcinoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):1861-6.

**AUTORES / AUTHORS:** - Ono M; Higuchi T; Takeshima M; Chen C; Nakano S

**INSTITUCIÓN / INSTITUTION:** - Ph.D. Graduate School of Health and Nutritional Sciences, Nakamura Gakuen University, Fukuoka, Fukuoka 814-0198, Japan. [snakano@nakamura-u.ac.jp](mailto:snakano@nakamura-u.ac.jp).

**RESUMEN / SUMMARY:** - Aim: Curcumin has potent antitumor activity against many types of human cancers. However, the inhibitory effects and possible mechanisms of curcumin on gallbladder cancer remains to be determined. MATERIALS AND METHODS: Using HAG-1 human gallbladder adenocarcinoma cells, we investigated the effects of curcumin on cell proliferation, apoptosis, cell-cycle perturbation, and signal proteins for survival, proliferation, and apoptosis. RESULTS: Curcumin exhibited dose-dependent antitumor activity against HAG-1 cells, arresting the cells in G2/M phase, with progressive expansion of the apoptotic cell population. Upon curcumin treatment, AKT activation was substantially suppressed, with subsequent reduction of activities of mammalian target of rapamycin (mTOR) and its downstream molecules S6 kinase-1 (S6K1) and eIF4E-binding protein-1 (4E-BP1), but constitutive activity of extracellular signal-regulated kinase (ERK1/2) was clearly enhanced. Curcumin reduced the expression and phosphorylation of anti-apoptotic Bcl-2, but did not affect the expressions of pro-apoptotic Bax and anti-apoptotic nuclear factor (NF-kappaB). CONCLUSION: These results suggest that curcumin induces G2/M arrest and apoptosis through multiple mechanisms involving enhanced mitogen-activated protein (MAP) kinase activity, reduced AKT-mTOR activity, and reduced Bcl-2 function. These data provide a mechanistic rationale for the potential use of curcumin in the treatment of gallbladder cancer.

[502]

**TÍTULO / TITLE:** - The histone deacetylase inhibitor trichostatin a promotes apoptosis and antitumor immunity in glioblastoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1351-60.

**AUTORES / AUTHORS:** - Horing E; Podlech O; Silkenstedt B; Rota IA; Adamopoulou E; Naumann U

**INSTITUCIÓN / INSTITUTION:** - Hertie Institute for Clinical Brain Research and Center Neurology, Department of Vascular Neurology, Laboratory of Molecular Neuro-Oncology, Tübingen, Germany.

**RESUMEN / SUMMARY:** - Histone deacetylase inhibitors (HDACi) have been described as multifunctional anticancer agents. The failure of conventional therapy for glioblastoma (GBM) renders this tumor an attractive target for immunotherapy. Innate immune cells, such as natural killer (NK) cells, play a crucial role in antitumor immune responses. Here, we describe how the HDACi trichostatin A (TSA) promotes apoptosis of tumor cells, as well as augments anti-GBM innate immune responses. In vitro treatment of GBM cells with TSA results in an up-regulation of the natural killer group-2 member-D (NKG2D) ligands major histocompatibility complex class I-related chain (MIC)-A and UL16 binding protein (ULBP)-2 at both mRNA and protein levels, rendering them susceptible to NK cell-mediated lysis. In vivo, TSA delays tumor growth of GBM xenografts. Both the in vitro and in vivo antitumor effect of TSA was significantly reduced by blocking NK cell activity. Our data suggest that HDACi, especially in combination with other clinical immunotherapeutic approaches, may be considered in a combined therapeutic approach for GBM.

[503]

**TÍTULO / TITLE:** - Effects of pyridine analogs of curcumin on growth, apoptosis and NF-kappaB activity in prostate cancer PC-3 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1343-50.

**AUTORES / AUTHORS:** - Wei X; Zhou D; Wang H; Ding N; Cui XX; Wang H; Verano M; Zhang K; Conney AH; Zheng X; DU ZY

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry and Chemical Engineering, Guangzhou University, Guangzhou, PR China.

**RESUMEN / SUMMARY:** - Twelve pyridine analogs of curcumin were studied for their effects on growth and apoptosis in human prostate cancer PC-3 cells. The ability of these compounds to inhibit the transcriptional activity of nuclear factor-kappa B (NF-kappaB) and the level of phosphorylated extracellular signal-regulated kinases (phospho-ERK1/2) in PC-3 cells was also determined. Treatment of PC-3 cells with the pyridine analogs of curcumin resulted in concentration-dependent growth inhibition and apoptosis stimulation. Only pyridine analogs of curcumin with a tetrahydrothiopyrane-4-one linker (FN compounds) exhibited a strong inhibitory effect on growth and a strong stimulatory effect on apoptosis at low concentrations ( $\leq 1 \mu\text{M}$ ). Mechanistic studies showed that NF-kappaB transcriptional activity in PC-3 cells was strongly inhibited by treatment with group FN compounds. Treatment of PC-3 cells with  $1 \mu\text{M}$  FN1 resulted in a decrease of activated ERK1/2. Results from

the present study indicate that FN compounds warrant further in vivo studies using suitable animal models of prostate cancer.

[504]

**TÍTULO / TITLE:** - Soluble FGL2 induced by tumor necrosis factor-alpha and interferon-gamma in CD4 T cells through MAPK pathway in human renal allograft acute rejection.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Surg Res. 2013 Apr 30. pii: S0022-4804(13)00354-5. doi: 10.1016/j.jss.2013.04.011.

●●Enlace al texto completo (gratis o de pago) [1016/j.jss.2013.04.011](#)

**AUTORES / AUTHORS:** - Zhao Z; Wang L; Yang C; Zhao T; Li L; Hu L; Wu D; Rong R; Xu M; Zhu T

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Zhongshan Hospital, Fudan University, Shanghai, China; Shanghai Key Laboratory of Organ Transplantation, Shanghai, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Acute rejection (AR), initiated by alloreactive CD4+ T cells, hampers allograft survival. Soluble fibrinogen-like protein 2 (sFGL2) is a novel effector of CD4+ T cells. We previously found that serum sFGL2 significantly increased in renal allograft recipients with AR. In this study, sFGL2 secretion by CD4+ T cells and its mechanism were further explored both in vivo and in vitro. MATERIALS AND METHODS: Forty cases of living-related renal transplant recipients with biopsy-proven AR or stable renal function were collected and detected serum sFGL2, tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma, and peripheral CD4+ T cells. In vitro, the isolated human CD4+ T cells were stimulated by TNF-alpha or IFN-gamma. sFGL2 in the supernatant and mitogen-activated protein kinase (MAPK) proteins in the CD4+ T cells were investigated. Approval for this study was obtained from the Ethics Committee of Fudan University. RESULTS: sFGL2, TNF-alpha, IFN-gamma, and CD4+ T cells were significantly increased in the peripheral blood of renal allograft recipients with AR. Stimulation with 1000 U/mL TNF-alpha or 62.5 U/mL IFN-gamma for 48 h provided an optimal condition for CD4+ T cells to secrete sFGL2 in vitro. Phosphorylated (p-) c-Jun N-terminal kinase was remarkably upregulated in the activated CD4+ T cells, whereas no significant changes were found in p-p38 MAPK or p-ERK1/2 expression. Furthermore, inhibition of c-Jun N-terminal kinase significantly reduced sFGL2 secretion by CD4+ T cells. CONCLUSIONS: sFGL2 secretion by CD4+ T cells can be induced with TNF-alpha and IFN-gamma stimulation through MAPK signaling in renal allograft AR. Our study suggests that sFGL2 is a potential mediator in the pathogenesis of allograft rejection.

[505]

**TÍTULO / TITLE:** - Raf kinase inhibitor protein (RKIP) and phospho-RKIP expression in melanomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Histochem. 2013 Apr 17. pii: S0065-1281(13)00053-6. doi: 10.1016/j.acthis.2013.03.003.

●●Enlace al texto completo (gratis o de pago)

[1016/j.acthis.2013.03.003](#)

**AUTORES / AUTHORS:** - Cardile V; Malaponte G; Loreto C; Libra M; Caggia S; Trovato FM; Musumeci G

**INSTITUCIÓN / INSTITUTION:** - Department of Bio-medical Sciences, Section of Physiology, University of Catania, Viale A. Doria 6, 95125 Catania, Italy.

**RESUMEN / SUMMARY:** - Melanoma, a cancer notorious for its high potential to metastasize, arises from melanocytes, cells dedicated to melanin production and located in the basal layer of the epidermis. Raf-1 kinase inhibitor protein (RKIP) is an inhibitory molecule that down-regulates the effects of the Ras/Raf/MEK/ERK signaling pathway. The aim of this study was to examine the expression of RKIP and pRKIP in melanomas at different stages. We evaluated the RKIP and pRKIP protein by immunohistochemistry in control skin, pigmented nevi and melanomas, and through Western blotting in human normal melanocytes and in four different melanoma-derived cell lines (WM35, A375, M14, and A2058). Our results demonstrated a correlation between the expression of RKIP and pRKIP, and metastatic ability in melanoma cells. This raises the possibility to analyze both RKIP and pRKIP in all melanomas. Down-regulation of both RKIP and pRKIP expression could represent a useful marker of metastatic melanoma. On the contrary for non-metastatic melanoma, especially in Clark I and II, low RKIP and high pRKIP expression could be indicative. In conclusion, the observed negative correlation of the RKIP and pRKIP expression in metastatic melanomas indicates that expression of these proteins may become a prognostic marker for the progression of human cutaneous melanoma. We propose that the investigation of both RKIP and pRKIP may provide a useful tool indicative for metastatic or non-metastatic melanoma in different Clark's level melanomas. Further studies are required to verify the molecular background of the observed RKIP and pRKIP variations.

[506]

**TÍTULO / TITLE:** - Human papillomavirus tumor-infiltrating T-regulatory lymphocytes and P53 codon 72 polymorphisms correlate with clinical staging and prognosis of oropharyngeal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - New Microbiol. 2013 Apr;36(2):133-44. Epub 2013 Mar 31.

**AUTORES / AUTHORS:** - Ritt M; Landolfo V; Mazibrada J; De Andrea M; Dell'oste V; Caneparo V; Peretti A; Giordano C; Pecorari G; Garzaro M; Landolfo S

**INSTITUCIÓN / INSTITUTION:** - Department of Public Health and Microbiology, Turin Medical School, Turin, Italy.

**RESUMEN / SUMMARY:** - The association between human papillomavirus (HPV) DNA positivity, p53 codon 72 polymorphisms, and the type of leukocyte infiltration in head and neck squamous cell carcinomas (HNSCC) and their combined impact upon patient survival is poorly investigated. For this reason, leukocyte infiltration profile and p53 codon 72 polymorphisms were assessed in freshly removed HNSCC specimens (N=71 patients). HPV detection was performed by nested-PCR followed by DNA sequencing. Viral loads were determined by quantitative RT-PCR. The choice to investigate fresh instead of archive paraffin-embedded specimens was privileged to avoid possible artifacts due to sample processing. HPV DNA was detected in 14% of cases. Oropharyngeal carcinomas were the most frequently associated with the presence of HPV16 DNA (41%) and were associated with p53 Pro/Pro or Pro/Arg polymorphisms. In HPV16-positive oropharyngeal carcinomas increased infiltrations of CD3+ and FoxP3+ T-cells correlated with higher HPV16 copy numbers. The presence of HPV may trigger a stronger immune response and may be considered a reliable marker for clinical staging and a more favorable prognosis of oropharyngeal carcinoma.

[507]

**TÍTULO / TITLE:** - Children and adolescents with follicular lymphoma have an excellent prognosis with either limited chemotherapy or with a “watch and wait” strategy after complete resection.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hematol. 2013 May 12.

●●Enlace al texto completo (gratis o de pago) [1007/s00277-013-1785-](http://1007/s00277-013-1785-2)

[2](#)

**AUTORES / AUTHORS:** - Attarbaschi A; Beishuizen A; Mann G; Rosolen A; Mori T; Uyttebroeck A; Niggli F; Csoka M; Krenova Z; Mellgren K; Kabickova E; Chiang AK; Reiter A; Williams D; Burkhardt B

**INSTITUCIÓN / INSTITUTION:** - Pediatric Hematology and Oncology, St. Anna Children's Hospital, Kinderspitalgasse 6, 1090, Vienna, Austria, [andishe.attarbaschi@stanna.at](mailto:andishe.attarbaschi@stanna.at).

**RESUMEN / SUMMARY:** - Data on clinical features and outcome in pediatric follicular lymphoma (pFL) are scarce. The aim of this retrospective study including 13 EICNHL and/or i-BFM study group members was to assess clinical characteristics and course in a series of 63 pFL patients. pFL was found to be associated with male gender (3:1), older age (72 %  $\geq 10$  years old), low serum LDH levels ( $< 500$  U/l in 75 %), grade 3 histology (in 88 %), and limited disease (87 % stage I/II disease), mostly involving the peripheral lymph nodes. Forty-four out of sixty-three patients received any polychemotherapy and 1/63 rituximab only, while 17/63 underwent a “watch and wait” strategy. Of 36 stage I

patients, 30 had complete resections. Only one patient relapsed; 2-year event-free survival and overall survival were 94 +/- 5 and 100 %, respectively, after a median follow-up of 2.2 years. Conclusively, treatment outcome in pFL seems to be excellent with risk-adapted chemotherapy or after complete resection and an observational strategy only.

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[508]

**TÍTULO / TITLE:** - A1E inhibits proliferation and induces apoptosis in NCI-H460 lung cancer cells via extrinsic and intrinsic pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1007/s11033-013-2544-0](#)

**AUTORES / AUTHORS:** - Bak Y; Ham S; Baatartsogt O; Jung SH; Choi KD; Han TY; Han IY; Yoon DY

**INSTITUCIÓN / INSTITUTION:** - Department of Bioscience and Biotechnology, Bio/Molecular Informatics Center, Konkuk University, Hwayang-dong 1, Gwangjin-gu, Seoul, 143-701, Republic of Korea.

**RESUMEN / SUMMARY:** - It has been reported that extracts from Asian traditional/medical herbs possess therapeutic agents against cancers, metabolic diseases, inflammatory diseases, and other intractable diseases. In this study, we assessed the molecular mechanisms involved in the anticancer effects of A1E, the extract of Korean medicinal herbs. We examined the role of the cytotoxic and apoptotic pathways in the cancer chemopreventive activity in non-small-cell lung cancer (NSCLC) cell lines NCI-H460 and NCI-H1299. A1E inhibited the proliferation of NCI-H460 more efficiently than NCI-H1299 (p53<sup>-/-</sup>) cells. The apoptosis was detected by nuclear morphological changes, annexin V-FITC/PI staining, cell cycle analysis, western blot, RT-PCR, and measurement of mitochondrial membrane potential. A1E induced cellular morphological changes and nuclear condensation at 24 h in a dose-dependent manner. A1E also perturbed cell cycle progression at the sub-G1 stage and altered cell cycle regulatory factors in NCI-H460 cells. Furthermore, A1E inhibited the PI3K/Akt and NF-kappaB survival pathways, and it activated apoptotic intrinsic and extrinsic pathways. A1E increased the expression levels of members of the extrinsic death receptor complex FasL and FADD. In addition, A1E treatment induced cleavage of caspase-8, caspase-9, caspase-3, and poly ADP-ribose polymerase (PARP), whereas the expression levels of Bcl-2 and Bcl-xl were downregulated. A1E induced mitochondrial membrane potential collapse and cytochrome C release. Our results suggest that A1E induces apoptosis via activation of both extrinsic and intrinsic pathways and inhibition of PI3K/Akt survival signaling pathways in NCI-H460 cells. In conclusion, these data demonstrate the potential of A1E as a novel chemotherapeutic agent in NSCLC.

[509]

**TÍTULO / TITLE:** - Glioma therapy using tumor homing and penetrating peptide-functionalized PEG-PLA nanoparticles loaded with paclitaxel.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomaterials. 2013 Jul;34(22):5640-50. doi: 10.1016/j.biomaterials.2013.04.025. Epub 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biomaterials.2013.04.025](#)

**AUTORES / AUTHORS:** - Hu Q; Gao X; Gu G; Kang T; Tu Y; Liu Z; Song Q; Yao L; Pang Z; Jiang X; Chen H; Chen J

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Smart Drug Delivery, Ministry of Education & PLA, School of Pharmacy, Fudan University, Lane 826, Zhangheng Road, Shanghai 201203, PR China.

**RESUMEN / SUMMARY:** - By taking advantage of the excessively upregulated expression of neuropilin (NRP) on the surface of both glioma cells and endothelial cells of angiogenic blood vessels, the ligand of NRP with high affinity - tLyp-1 peptide, which also contains a CendR motif ((R/K)XX(R/K)), was functionalized to the surface of PEG-PLA nanoparticles (tLyp-1-NP) to mediate its tumor homing, vascular extravasation and deep penetration into the glioma parenchyma. The tLyp-1-NP was prepared via a maleimide-thiol coupling reaction with uniformly spherical shape under TEM and particle size of 111.30 +/- 15.64 nm. tLyp-1-NP exhibited enhanced cellular uptake in both human umbilical vein endothelial cells and Rat C6 glioma cells, increased cytotoxicity of the loaded PTX, and improved penetration and growth inhibition in avascular C6 glioma spheroids. Selective accumulation and deep penetration of tLyp-1-NP at the glioma site was confirmed by in vivo imaging and glioma distribution analysis. The longest survival was achieved by those mice bearing intracranial C6 glioma treated with PTX-loaded tLyp-1-NP. The findings here strongly indicate that tLyp-1 peptide-functionalized nanoparticulate DDS could significantly improve the efficacy of paclitaxel glioma therapy.

[510]

**TÍTULO / TITLE:** - IFN-gamma selectively exerts pro-apoptotic effects on tumor-initiating label-retaining colon cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 May 2. pii: S0304-3835(13)00363-7. doi: 10.1016/j.canlet.2013.04.029.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.04.029](#)

**AUTORES / AUTHORS:** - Ni C; Wu P; Zhu X; Ye J; Zhang Z; Chen Z; Zhang T; Zhang T; Wang K; Wu D; Qiu F; Huang J

**INSTITUCIÓN / INSTITUTION:** - Cancer Institute (Key Laboratory of Cancer Prevention & Intervention, National Ministry of Education, Provincial Key Laboratory of Molecular Biology in Medical Sciences), The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China.

**RESUMEN / SUMMARY:** - Label-retaining cancer cells (LRCCs) represent a novel population of stem-like cancer cells exhibiting slow cycling, chemoresistance and tumor-initiating capacities; however, their properties remain unclear, and approaches to eradicate LRCCs remain elusive. Here, we report that colon cancer cells with high fluorescent intensity, referred to as LRCCs, have the greatest cancer stem cell (CSC)-like capacities and that they preferentially express CSC markers and stemness-related genes. Moreover, we found that Lgr5, which has been reported to be a marker of rapid cycling CSCs, is almost negatively expressed in LRCCs but that its expression is gradually increased in the differentiation process of LRCCs. Interestingly, we found that LRCCs are especially sensitive to the pro-apoptotic effect of IFN-gamma treatment both in vitro and in vivo because LRCCs possess higher IFN-gammaR levels compared with non-LRCCs, which results in the upregulation of the apoptosis pathway after IFN-gamma treatment. Furthermore, we found that IFN-gamma shows synergistic effects with the conventional anticancer drug Oxaliplatin to eliminate both LRCCs and non-LRCCs. In conclusion, this is the first study to suggest that LRCCs, as a distinct tumor-initiating population, can be selectively eradicated by IFN-gamma, which may provide a novel therapeutic strategy for colon cancer treatment.

[511]

**TÍTULO / TITLE:** - Increased expression of ALDH1A1 protein is associated with poor prognosis in clear cell renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):574. doi: 10.1007/s12032-013-0574-z. Epub 2013 Apr 13.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0574-](#)

[Z](#)

**AUTORES / AUTHORS:** - Wang K; Chen X; Zhan Y; Jiang W; Liu X; Wang X; Wu B

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Sheng Jing Hospital of China Medical University, Shenyang 110004, Liaoning, People's Republic of China.

**RESUMEN / SUMMARY:** - Aldehyde dehydrogenase 1A1 (ALDH1A1) has been characterized as a cancer stem cell marker in different types of tumors. It plays a key role in various biological processes in tumor, including cell proliferation, invasion and chemoresistance. Recently, ALDH1A1 has been described as a prognostic marker in various tumors. In this study, we detected the expression of ALDH1A1 in 95 clear cell renal cell carcinoma (ccRCC) by

immunohistochemistry and correlated it with clinicopathological parameters and prognosis. We further explored the correlation of ALDH1A1 expression to proliferation, invasion and drug sensitivity of renal cancer cell in vitro by silencing of ALDH1A1 in A498 renal cell line. ALDH1A1 protein showed high expression in 53 of 95 cases of ccRCC (56.8 %), which was significantly higher than that in normal tissues (5/23, 21.7 %). ALDH1A1 overexpression was significantly associated with tumor stage ( $P = 0.000$ ), recurrence ( $P = 0.000$ ), tumor size ( $P = 0.000$ ) and vascular invasion ( $P = 0.023$ ). The Kaplan-Meier survival analysis demonstrated that ALDH1A1 overexpression was significantly associated with shorter recurrence-free survival and overall survival ( $P = 0.003$  and  $P = 0.008$ , respectively). Multivariate analysis demonstrated that ALDH1A1 was an independent prognostic factor for patients with ccRCC. Experiments in vitro further showed ALDH1A1 played an essential role in proliferation, invasion and drug sensitivity of renal cancer cell. In conclusion, ALDH1A1 might be a potential molecular marker in ccRCC, which provided us with a new therapeutic target in ccRCC.

[512]

**TÍTULO / TITLE:** - Telekin induces apoptosis associated with the mitochondria-mediated pathway in human hepatocellular carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biol Pharm Bull. 2013 May 9.

**AUTORES / AUTHORS:** - Zheng B; Wu L; Ma L; Liu S; Li L; Xie W; Li X

**INSTITUCIÓN / INSTITUTION:** - School of Ocean, Shandong University.

**RESUMEN / SUMMARY:** - Telekin, a eudesmane-type sesquiterpene lactone compound isolated from Chinese folk medicine *Carpesium divaricatum*, has been reported to strongly inhibit the proliferation of cancer cells. In this study, the involvement of a mitochondria-mediated pathway in the pro-apoptotic action of telekin was investigated in human hepatocellular carcinoma cells. MTT assays showed that telekin exhibited excellent anti-proliferation activity in hepatocellular carcinoma cells and low cytotoxicity to normal hepatocyte cells. Telekin-induced apoptosis was characterized by chromatin condensation, formation of apoptotic bodies, and exposure of phosphatidylserine on the extracellular surface, as revealed by DAPI nuclear staining and flow cytometry. Flow cytometry analysis showed that telekin induced the loss of mitochondrial membrane potential (MMP), as well as increased the levels of intracellular free calcium and reactive oxygen species (ROS). Additionally, Western blot results demonstrated that telekin induced the decrease in Apaf-1 and Bcl-2 expression, increase in Bax expression, release of cytochrome C, and activation of caspase-9 and caspase-3 in HepG-2 cells. These findings indicate that telekin activates the mitochondria-mediated apoptotic pathway in hepatocellular carcinoma cells and may merit further investigation as a potential therapeutic agent for the treatment of hepatocellular carcinoma.

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[513]

**TÍTULO / TITLE:** - Tumor suppressor BLU promotes paclitaxel antitumor activity by inducing apoptosis through the down-regulation of Bcl-2 expression in tumorigenesis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 24;435(1):153-9. doi: 10.1016/j.bbrc.2013.04.061. Epub 2013 Apr 27.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.04.061](http://1016/j.bbrc.2013.04.061)

**AUTORES / AUTHORS:** - Park ST; Byun HJ; Kim BR; Dong SM; Park SH; Jang PR; Rho SB

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Kangnam Sacred Heart Hospital, Hallym University, 948-1, Daerim 1-dong, Yeongdeungpo-gu, Seoul 150-950, Republic of Korea.

**RESUMEN / SUMMARY:** - In this current work, we investigated whether BLU could enhance pro-apoptotic activity of chemotherapeutic drugs in ovarian carcinoma cells. A combination with a chemotherapeutic drug showed an additive effect, and this additive effect was supplemented by the enhancement of caspase-3 and -9 activities. BLU and paclitaxel induced cell cycle arrest in the G2/M phase through the reduction of cyclin dependent kinase 1, cyclin B1, while promoting both p16 and p27 expression. In addition, both BLU and paclitaxel enhanced the expression of the pro-apoptotic protein Bax together with the suppression of anti-apoptotic protein Bcl-2, a protein which is well-known for its function as a regulator in protecting cells from apoptosis. As expected, the Bax and p21 activities were enhanced by BLU or paclitaxel, while a combination of BLU and paclitaxel were additively promoted, whereas Bcl-xL and NF-kappaB including Bcl-2 activity were inactivated. This study has yielded promising results, which evidence for the first time that BLU could suppress the growth of carcinoma cells. Furthermore, both BLU and paclitaxel inhibited the phosphorylation of signaling components downstream of phosphoinositide 3-kinase, such as 3-phosphoinositide-dependent protein kinase 1, and Akt. Also, BLU plus paclitaxel decreased phosphorylation of p70 ribosomal S6 kinase, as well as decreasing the phosphorylation of glycogen synthase kinase-3beta, which is one of the representative targets of the mammalian target of rapamycin signaling cascade. These results provide evidence that BLU enhances G2/M cell cycle arrest and apoptotic cell death through the up-regulation of Bax, p21 and p53 expression.

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[514]

**TÍTULO / TITLE:** - Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 May 28. doi: 10.1002/ijc.28284.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28284](http://1002/ijc.28284)

**AUTORES / AUTHORS:** - Sheng L; Luo M; Sun X; Lin N; Mao W; Su D

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Therapy, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China; Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Zhejiang, China.

**RESUMEN / SUMMARY:** - Serum fibrinogen converted to insoluble fibrin by activated thrombin, plays an important role in the coagulation system. Increased fibrinogen considerably influences cancer cell growth, progression and metastasis. In nonsmall cell lung cancer (NSCLC), however, the association between serum fibrinogen concentration and prognosis has not been fully examined. We enlisted 567 operable NSCLC patients in this study.

Preoperative serum fibrinogen was measured by the Clauss method. The association of serum fibrinogen concentration with clinical pathological factors and patient outcome was evaluated. Survival analysis indicated that serum fibrinogen was an independent prognostic factor in operable NSCLC. Patients with hyperfibrinogenemia had an elevated risk of disease progression and death compared with patients with normal fibrinogen levels. The hazard ratio was 1.49 (95% confidence interval [CI] 1.07-2.05) for disease progression and 1.64 (95% CI 1.06-2.53) for death. The trend linking increasing fibrinogen levels with risk was also statistically significant for both outcomes ( $p < 0.05$ ). These analyses were adjusted for patient age, sex, smoking behavior, disease stage, tumor grade and histology. Kaplan-Meier survival curves showed similar results. Preoperative serum fibrinogen is a novel independent prognostic biomarker in operable NSCLC. © 2013 Wiley Periodicals, Inc.

[515]

**TÍTULO / TITLE:** - Resveratrol induces cell death in cervical cancer cells through apoptosis and autophagy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer Prev. 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago)

[1097/CEJ.0b013e328360345f](http://1097/CEJ.0b013e328360345f)

**AUTORES / AUTHORS:** - Garcia-Zepeda SP; Garcia-Villa E; Diaz-Chavez J; Hernandez-Pando R; Gariglio P

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Genetics and Molecular Biology, Center for Research and Advance Studies, National Polytechnic Institute bUnit of Biomedical Research in Cancer, Institute of Biomedical Research, UNAM/National Cancer Institute cDepartment of Experimental Pathology, National Institute for Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico.

**RESUMEN / SUMMARY:** - Cervical neoplasia is one of the most frequent cancers in women and is associated with high-risk human papillomavirus (HPV) infection. Resveratrol, a natural polyphenolic phytochemical, has received

considerable interest on the basis of its potential as a chemopreventive agent against human cancer. In this work, we analyzed the type of cell death induced by resveratrol in several cervical cancer cell lines. Resveratrol treatment (150-250 micromol/l) for 48 h increased cell cycle arrest at the G1 phase in C33A (with mutation in p53) and HeLa cells (HPV18 positive), as well as in CaSki and SiHa cell lines (HPV16 positive). Resveratrol treatment induced apoptosis in all cell lines, particularly in CaSki cells, as measured by Annexin-V flow cytometry analysis. There was a decrease in the mitochondrial membrane potential (apoptosis) in HeLa, CaSki, and SiHa cells and an increased lysosomal permeability (autophagy) in C33A, CaLo (HPV18 positive), and HeLa cell lines. Furthermore, when we used the IC50 of each line, we found that resveratrol produces a similar effect, suggesting that this effect is not dependent on the concentration of resveratrol. Interestingly, after resveratrol treatment, the expression of p53 was decreased in HPV18-positive cell lines (CaLo and HeLa) and increased in HPV16-positive cell lines (CaSki and SiHa) and C33A cells. The expression of p65 (an NF-kappaB subunit) was decreased after treatment in all cell lines except SiHa cells. These data indicate that resveratrol uses different mechanisms to induce cell death in cell lines derived from cervical cancer.

[516]

**TÍTULO / TITLE:** - Heterodimeric Bispecific Single-Chain Variable-Fragment Antibodies Against EpCAM and CD16 Induce Effective Antibody-Dependent Cellular Cytotoxicity Against Human Carcinoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biother Radiopharm. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1089/cbr.2012.1329](#)

**AUTORES / AUTHORS:** - Vallera DA; Zhang B; Gleason MK; Oh S; Weiner LM; Kaufman DS; McCullar V; Miller JS; Verneris MR

**INSTITUCIÓN / INSTITUTION:** - 1 Section of Molecular Cancer Therapeutics, Therapeutic Radiology-Radiation Oncology, University of Minnesota Masonic Cancer Center, Minneapolis, Minnesota.

**RESUMEN / SUMMARY:** - Abstract A heterodimeric bispecific biological recombinant drug was synthesized by splicing DNA fragments from two fully humanized single-chain variable-fragment (scFV) antibody fragments forming a novel drug simultaneously recognizing the CD16 natural killer (NK) cell marker and the cancer marker epithelial cell adhesion molecule (EpCAM). The drug precipitously enhanced the killing of human carcinomas of the prostate, breast, colon, head, and neck even at very low effector:target ratios. The drug EpCAM16 rendered even nonactivated NK cell-proficient killers and activated them to kill via degranulation and cytokine production. Studies show that bispecific antibodies can be used to induce proficient killing of the carcinoma targets that ordinarily are resistant to NK-mediated killing. Apparently, the innate

immune system can be effectively recruited to kill cancer cells using the bispecific antibody platform and EpCAM targeting.

[517]

**TÍTULO / TITLE:** - In vitro cytotoxicity of *Gymnema montanum* in human leukaemia HL-60 cells; induction of apoptosis by mitochondrial membrane potential collapse.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Prolif. 2013 Jun;46(3):263-71. doi: 10.1111/cpr.12033.

●●Enlace al texto completo (gratis o de pago) [1111/cpr.12033](#)

**AUTORES / AUTHORS:** - Ramkumar KM; Manjula C; Elango B; Krishnamurthi K; Saravana Devi S; Rajaguru P

**INSTITUCIÓN / INSTITUTION:** - SRM Research Institute, SRM University, Kattankulathur, 603 203, India.

**RESUMEN / SUMMARY:** - **OBJECTIVES:** *Gymnema montanum* Hook, an Indian Ayurvedic medicinal plant, is used traditionally to treat a variety of ailments. Here, we report anti-cancer effects and molecular mechanisms of ethanolic extract of *G. montanum* (GLEt) on human leukaemia HL-60 cells, compared to peripheral blood mononuclear cells. **MATERIALS AND METHODS:** HL-60 cells were treated with different concentrations of GLEt (10-50 µg/ml) and cytotoxicity was assessed by MTT assay. Levels of lipid peroxidation, antioxidants, mitochondrial membrane potential and caspase-3 were measured. Further, apoptosis was studied using annexin-V staining and the cell cycle was analyzed by flow cytometry. **RESULTS:** GLEt had a potent cytotoxic effect on HL-60 cells (IC<sub>50</sub> -20 µg/ml), yet was not toxic to normal peripheral blood mononuclear cells. Exposure of HL-60 cells to GLEt led to elevated levels of malonaldehyde formation, but to reduced glutathione, superoxide dismutase, catalase and glutathione peroxidase activities (P < 0.05). Induction of apoptosis was confirmed by observing annexin-V positive cells, associated with loss of mitochondrial membrane potential. Cell cycle arrest at G<sub>0</sub>/G<sub>1</sub> was observed in GLEt-treated HL-60 cells, indicating its potential at inducing their apoptosis. **CONCLUSIONS:** Findings of the present study suggest that *G. montanum* induced apoptosis in the human leukaemic cancer cells, mediated by collapse of mitochondrial membrane potential, generation of reactive oxygen species and depletion of intracellular antioxidant potential.

[518]

**TÍTULO / TITLE:** - New findings of kinase switching in gastrointestinal stromal tumor under imatinib using phosphoproteomic analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 May 28. doi: 10.1002/ijc.28282.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28282](https://doi.org/10.1002/ijc.28282)

**AUTORES / AUTHORS:** - Takahashi T; Serada S; Ako M; Fujimoto M; Miyazaki Y; Nakatsuka R; Ikezoe T; Yokoyama A; Taguchi T; Shimada K; Kurokawa Y; Yamasaki M; Miyata H; Nakajima K; Takiguchi S; Mori M; Doki Y; Naka T; Nishida T

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Osaka University Graduate School of Medicine, Suita, Japan; Laboratory for Immune Signal, National Institute of Biomedical Innovation, Ibaraki, Japan.

**RESUMEN / SUMMARY:** - Despite the revolutionary effects of imatinib on advanced gastrointestinal stromal tumors (GISTs), most patients eventually develop disease progression following primary resistance or acquired resistance driven by secondary-resistant mutations. Even in radiographically vanishing lesions, pathology has revealed persistent viable cells during imatinib therapy, which could lead to the emergence of drug-resistant clones. To uncover the mechanisms underlying these clinical issues, here we examined imatinib-induced phosphoproteomic alterations in GIST-T1 cells, using our quantitative tyrosine phosphoproteomic analysis method, which combined immunoaffinity enrichment of phosphotyrosine-containing peptides with iTRAQ technology. Using this approach, we identified 171 tyrosine phosphorylation sites spanning 134 proteins, with 11 proteins exhibiting greater than 1.5-fold increases in tyrosine phosphorylation. Among them, we evaluated FYN and focal adhesion kinase (FAK), both of which are reportedly involved in proliferation and malignant alteration of tumors. We confirmed increased tyrosine phosphorylation of both kinases by western blotting. Inhibition of FYN and FAK phosphorylation each increased tumor cell sensitivity to imatinib. Furthermore, a FAK-selective inhibitor (TAG372) induced apoptosis of imatinib-resistant GIST-T1 cells and decreased the imatinib IC<sub>50</sub>. These results indicate that FYN or FAK might be potential therapeutic targets to overcome resistance to imatinib in GISTs. Additionally, we showed that the iTRAQ-based quantitative phosphotyrosine-focused phosphoproteomic approach is a powerful method for screening phosphoproteins associated with drug resistance. © 2013 Wiley Periodicals, Inc.

[519]

**TÍTULO / TITLE:** - Aspirin enhances IFN- $\alpha$ -induced growth inhibition and apoptosis of hepatocellular carcinoma via JAK1/STAT1 pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Gene Ther. 2013 May 24. doi: 10.1038/cgt.2013.29.

●●Enlace al texto completo (gratis o de pago) [1038/cgt.2013.29](https://doi.org/10.1038/cgt.2013.29)

**AUTORES / AUTHORS:** - Li T; Dong ZR; Guo ZY; Wang CH; Tang ZY; Qu SF; Chen ZT; Li XW; Zhi XT

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Qilu Hospital, Shandong University, Jinan, China.

**RESUMEN / SUMMARY:** - STAT1 has a key role in exerting the antiproliferative and proapoptotic effects of interferon (IFN)-alpha on tumors, and its defects in expression is associated with IFN-alpha resistance. In this study we want to investigate whether aspirin can improve the antitumor efficiency of IFN-alpha on hepatocellular carcinoma (HCC) through the activation of STAT1. We found that aspirin not only significantly enhanced IFN-alpha-induced antiproliferation and apoptosis of HCC in vitro study but also enhanced tumor growth inhibition in nude mice. Although IFN-alpha alone resulted in significant phosphorylation of both STAT1 and STAT3, aspirin only prompted the IFN-alpha-induced phosphorylation of STAT1. Further study revealed that aspirin-prompted phosphorylation of STAT1 was activated through phosphorylation of JAK1. Furthermore, aspirin-activated STAT1 upregulated the transcription of proapoptotic IFN-stimulated gene (ISG) of X-linked inhibitor of apoptosis-associated factor-1 and downregulated the transcription of antiapoptotic ISG of G1P3, which in turn promoted the expression of Bax and activation of caspase-9 and caspase-3, thereby sensitizing HCC cells to IFN-alpha-induced apoptosis. Taken together, our findings suggest a novel strategy of using aspirin to overcome tumor resistance and enhance the effectiveness of IFN-alpha in HCC treatment through activating STAT1 gene, and have potential implications for improving future IFN-alpha protein and gene therapy. Cancer Gene Therapy advance online publication, 24 May 2013; doi:10.1038/cgt.2013.29.

[520]

**TÍTULO / TITLE:** - Colon Cancer-Specific Cytochrome P450 2W1 Converts Duocarmycin Analogues into Potent Tumor Cytotoxins.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Jun 1;19(11):2952-61. doi: 10.1158/1078-0432.CCR-13-0238. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0238](#)

**AUTORES / AUTHORS:** - Travica S; Pors K; Loadman PM; Shnyder SD; Johansson I; Alandas MN; Sheldrake HM; Mkrtchian S; Patterson LH; Ingelman-Sundberg M

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Physiology and Pharmacology, Section of Pharmacogenetics, Karolinska Institutet, Stockholm, Sweden; and The Institute of Cancer Therapeutics, University of Bradford, Bradford, United Kingdom.

**RESUMEN / SUMMARY:** - PURPOSE: Cytochrome P450 2W1 (CYP2W1) is a monooxygenase detected in 30% of colon cancers, whereas its expression in nontransformed adult tissues is absent, rendering it a tumor-specific drug target for development of novel colon cancer chemotherapy. Previously, we have

identified duocarmycin synthetic derivatives as CYP2W1 substrates. In this study, we investigated whether two of these compounds, ICT2705 and ICT2706, could be activated by CYP2W1 into potent antitumor agents. EXPERIMENTAL DESIGN: The cytotoxic activity of ICT2705 and ICT2706 in vitro was tested in colon cancer cell lines expressing CYP2W1, and in vivo studies with ICT2706 were conducted on severe combined immunodeficient mice bearing CYP2W1-positive colon cancer xenografts. RESULTS: Cells expressing CYP2W1 suffer rapid loss of viability following treatment with ICT2705 and ICT2706, whereas the CYP2W1-positive human colon cancer xenografts display arrested growth in the mice treated with ICT2706. The specific cytotoxic metabolite generated by CYP2W1 metabolism of ICT2706 was identified in vitro. The cytotoxic events were accompanied by an accumulation of phosphorylated H2A.X histone, indicating DNA damage as a mechanism for cancer cell toxicity. This cytotoxic effect is most likely propagated by a bystander killing mechanism shown in colon cancer cells. Pharmacokinetic analysis of ICT2706 in mice identified higher concentration of the compound in tumor than in plasma, indicating preferential accumulation of drug in the target tissue. CONCLUSION: Our findings suggest a novel approach for treatment of colon cancer that uses a locoregional activation of systemically inactive prodrug by the tumor-specific activator enzyme CYP2W1. Clin Cancer Res; 19(11); 2952-61. ©2013 AACR.

[521]

**TÍTULO / TITLE:** - Predictive biomarkers for bevacizumab: are we there yet?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Jun 1;19(11):2824-7. doi: 10.1158/1078-0432.CCR-12-3409. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3409](#)

**AUTORES / AUTHORS:** - Maru D; Venook AP; Ellis LM

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Pathology and Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and Division of Medical Oncology, Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, California.

**RESUMEN / SUMMARY:** - Therapy targeting VEGF has become the standard of care in several solid malignancies. Early investigations attempting to identify predictive markers for the efficacy of therapy failed to identify any predictive markers that could help oncologists decide who should-and, more importantly, who should not-receive VEGF-targeted therapies. However, interest has been renewed in predictive biomarkers for VEGF-targeted therapies, especially in light of the fact that the U.S. Food and Drug Administration withdrew approval for use of bevacizumab, an antibody to VEGF, in patients with metastatic breast

cancer. In a recent publication in the Journal of Clinical Oncology, investigators identified circulating VEGF and tumor neuropilin-1 expression as potential predictive biomarkers for bevacizumab. From this perspective, we provide a critical evaluation of the use of these markers and the need for validation in prospective clinical trials. Clin Cancer Res; 19(11); 2824-7. ©2013 AACR.

[522]

**TÍTULO / TITLE:** - Decitabine, a DNA methyltransferases inhibitor, induces cell cycle arrest at G2/M phase through p53-independent pathway in human cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 May;67(4):305-11. doi: 10.1016/j.biopha.2013.01.004. Epub 2013 Feb 14.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2013.01.004](http://1016/j.biopha.2013.01.004)

**AUTORES / AUTHORS:** - Shin DY; Sung Kang H; Kim GY; Kim WJ; Yoo YH; Choi YH

**INSTITUCIÓN / INSTITUTION:** - Dongnam Institute of Radiological & Medicine Sciences, Busan 619-953, Republic of Korea; Department of Molecular Biology, Pusan National University, Busan 609-735, Republic of Korea.

**RESUMEN / SUMMARY:** - Decitabine (5-aza-2'-deoxycytidine), an inhibitor of DNA methyltransferases, has a wide range of anti-metabolic and anti-cancer activities. Decitabine also induces cell cycle arrest at G2/M phase and apoptosis in human cancer cells. However, the cellular and molecular mechanisms of this cell cycle arrest are poorly understood. In the present study, we investigated the roles of the tumor suppressor p53 and the cyclin-dependent kinase (Cdk) inhibitor p21 following decitabine-induced G2/M arrest in human cancer cells. DNA flow cytometric analyses indicated that decitabine induced a G2/M arrest in AGS gastric and A549 lung carcinoma cell lines, which have wild type p53. Western blot analyses using whole cell lysates from AGS cells demonstrated that decitabine treatment did not change the steady-state level of Cdks and Cdk inhibitor p27, but it partially inhibited expression of cyclin A, cyclin B1, and Cdc25C proteins. However, similar results were found using the A549 cell line, where decitabine induced a dramatic up-regulation of both p53 and p21 expression, and the increased levels of p21 were associated with increased binding of p21 with Cdks, cyclin A, and cyclin B1. Knockdown of p53 by small interfering RNA (siRNA) markedly abolished p53 induction by decitabine in AGS cells, yet p53 siRNA had no attenuating effect on p21 induction. In addition, depletion of p21 expression with siRNA, but not p53, significantly attenuated decitabine-induced G2/M arrest. We also observed that decitabine strongly induced G2/M arrest associated with p21 induction in both p53 allele-null (-/-) HCT116 and wild type p53 (+/+) HCT116 cell lines.

Therefore, our data indicated that p21 plays a crucial role in decitabine-induced G2/M arrest and operates in a p53-independent manner.

[523]

**TÍTULO / TITLE:** - Variability of Apoptosis and Response in N1-S1 Rodent Hepatomas to Benzamide Riboside and Correlation to Early Changes in Water Apparent Diffusion Coefficient and Sodium MR Imaging.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Vasc Interv Radiol. 2013 Jun;24(6):894-900. doi: 10.1016/j.jvir.2013.02.011. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1016/j.jvir.2013.02.011](#)

**AUTORES / AUTHORS:** - Faramarzian A; McLennan G; Bennett SL; Babsky A; Bansal N; Lieber M; Bonnac L; Pankiewicz K; Jayaram HN

**INSTITUCIÓN / INSTITUTION:** - Case Western Reserve University School of Medicine, Cleveland Clinic, Cleveland, Ohio. Electronic address: [axf227@case.edu](mailto:axf227@case.edu).

**RESUMEN / SUMMARY:** - PURPOSE: This pilot trial assesses variability of apoptosis and response 1 day after hepatic intraarterial (IA) benzamide riboside (BR) in rodent hepatomas and its correlation to water apparent diffusion coefficient (ADC) and single-quantum (SQ) and triple-quantum-filtered (TQF) sodium-23 (<sup>23</sup>Na) magnetic resonance (MR) imaging. MATERIALS AND METHODS: Sprague-Dawley rats (n = 8) were inoculated with 10(6) N1-S1 cells. IA BR (20 mg/kg) was infused after 14 days. Animals were killed 1 day (n = 4) or 21 days (n = 4) after therapy. Imaging was performed 1 day before and after treatment. Volume was assessed over 2 weeks. Percentage apoptosis was counted from terminal deoxynucleotidyl transferase dUTP nick-end labeling-stained slides at 400xmagnification. Kruskal-Wallis tests were used to compare apoptosis, and Wilcoxon signed-rank tests were used to compare MR signal intensity (SI). RESULTS: Apoptosis was marginally greater in tumor than in nontumor (6.7% vs 1.3%; P = .08), varying from 2% to 10%. Before treatment, MR SI was greater in tumor than in nontumor (ADC, 1.18 vs 0.76 [P = .0078]; SQ, 1.20 vs 1.04 [P = .03]; TQF, 0.55 vs 0.34 [P = .03]). After treatment, tumors increased in volume (0.62 vs 0.33; P = .016) variably over 2 weeks. MR SI remained greater in tumor than in nontumor (ADC, 1.20 vs 0.77 [P = .0078]; SQ, 1.76 vs 1.15 [P = .016]; TQF, 0.84 vs 0.49 [P = .03]). SQ and TQF SI increased by 47% (P = .016) and 53% (P = .016) in tumors, whereas ADC did not change. CONCLUSIONS: Apoptosis was marginal and varied from 2% to 10%. Water ADC, SQ, and TQF MR imaging distinguished tumor from nontumor. Changes in water ADC and sodium MR imaging correlated to apoptosis and volume in select cases, but additional animals are needed to validate this trend against tumor growth.

[524]

**TÍTULO / TITLE:** - Ring-substituted analogs of 3,3'-diindolylmethane (DIM) induce apoptosis and necrosis in androgen-dependent and -independent prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Invest New Drugs. 2013 May 25.

●●Enlace al texto completo (gratis o de pago) [1007/s10637-013-9979-](#)

[y](#)

**AUTORES / AUTHORS:** - Goldberg AA; Titorenko VI; Beach A; Abdelbaqi K; Safe S; Sanderson JT

**INSTITUCIÓN / INSTITUTION:** - INRS - Institut Armand-Frappier, Université du Québec, 531 boulevard des Prairies, Laval, QC, Canada.

**RESUMEN / SUMMARY:** - We recently reported that novel ring-substituted analogs of 3,3'-diindolylmethane (ring-DIMs) have anti-androgenic and growth inhibitory effects in androgen-dependent prostate cancer cells. The objectives of this study were to confirm the ability of 4,4'- and 7,7'-dibromo- and dichloro-substituted ring-DIMs to inhibit androgen-stimulated proliferation of androgen-dependent LNCaP human prostate cancer cells using a non-invasive, real-time monitoring technique. In addition, their ability to induce apoptotic and necrotic cell death in androgen-dependent as well as -independent (PC-3) prostate cancer cells was studied. Prostate cancer cells were treated with increasing concentrations of DIM and ring-DIMs (0.3-30  $\mu$ M) and effects on cell proliferation were measured in real-time using an xCELLigence cellular analysis system. Chromatin condensation and loss of membrane integrity were determined by Hoechst and propidium iodide staining, respectively. Apoptotic protein markers were measured by immunoblotting and activation of caspases determined using selective fluorogenic substrates. Intra- and extracellular concentrations of DIM and ring-DIMs were assessed by electrospray ionization tandem mass spectrometry. Ring-DIMs inhibited androgen-stimulated LNCaP cell proliferation and induced apoptosis and necrosis in LNCaP and PC-3 cells with 2-4 fold greater potencies than DIM. DIM and the ring-DIMs increased caspases -3, -8 and -9 activity, elevated expression of Fas, FasL, DR4 and DR5 protein, and induced PARP cleavage in both cell lines. The cytotoxicity of the most potent ring-DIM, 4,4'-dibromoDIM, but not the other compounds was decreased by an inhibitor of caspase -3. The 4,4'-dibromoDIM was primarily found in the extracellular medium, whereas all other compounds were present to a much larger extent in the cell. In conclusion, ring-DIMs inhibited prostate cancer cell growth and induced cell death in LNCaP and PC-3 cells with greater potencies than DIM; they also structure-dependently activated different cell death pathways suggesting that these compounds have clinical potential as chemopreventive and chemotherapeutic agents in prostate cancer, regardless of hormone-dependency.

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[525]

**TÍTULO / TITLE:** - Oxidative stress mediates apoptotic effects of ascorbate and dehydroascorbate in human Myelodysplasia cells in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Toxicol In Vitro. 2013 Aug;27(5):1542-9. doi: 10.1016/j.tiv.2013.03.009. Epub 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.03.009](http://1016/j.tiv.2013.03.009)

**AUTORES / AUTHORS:** - Goncalves AC; Alves V; Silva T; Carvalho C; Oliveira CR; Sarmiento-Ribeiro AB

**INSTITUCIÓN / INSTITUTION:** - Applied Molecular Biology and Hematology University Clinic, Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal; Centre of Investigation in Environment, Genetics and Oncobiology (CIMAGO), Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal; Centre for Neuroscience and Cell Biology (CNC), University of Coimbra, 3004-504 Coimbra, Portugal.

**RESUMEN / SUMMARY:** - The Myelodysplastic Syndromes are stem cell heterogeneous disorders characterized by peripheral cytopenias and hypercellular bone marrow, which can evolve to acute leukaemia. Vitamin C can act as an antioxidant, ascorbic acid (AA) donates two electrons and becomes oxidized to dehydroascorbic acid (DHA). Under physiological conditions, vitamin C predominantly exists in its reduced (AA) form but also exists in trace quantities in the oxidized form (DHA). This study evaluates the therapeutic potential of vitamin C in Myelodysplastic Syndromes (MDSs). F36P cells (MDS cell line) were treated with ascorbate and dehydroascorbate alone and in combination with cytarabine. Cell proliferation and viability were assessed by trypan blue assay and cell death was evaluated by optical microscopy and flow cytometry. The role of reactive oxygen species, mitochondrial membrane potential, BAX, BCL-2 and cytochrome C were also assessed. Vitamin C decreases cell proliferation and viability in a concentration, time and administration dependent-manner inducing cell death by apoptosis, which was shown to be associated to an increased in superoxide production, mitochondrial membrane depolarization. These compounds modulate BCL-2, BAX and cytochrome C release. These results suggest that vitamin C induces cell death through apoptosis in F36P cells and may be a new therapeutic approach in Myelodysplasia.

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[526]

**TÍTULO / TITLE:** - Combination therapy of portal vein resection and adjuvant gemcitabine improved prognosis of advanced pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatogastroenterology. 2013 Mar-Apr;60(122):354-7. doi: 10.5754/hge12614.

●●Enlace al texto completo (gratis o de pago) [5754/hge12614](http://5754/hge12614)

**AUTORES / AUTHORS:** - Nakamura M; Kayashima T; Fujiwara K; Nagayoshi Y; Kono H; Ohtsuka T; Takahata S; Mizumoto K; Tanaka M

**RESUMEN / SUMMARY:** - Background/Aims: Although adjuvant chemotherapy (AC) using gemcitabine improves the prognosis of patients with resectable pancreatic cancer, the effect of gemcitabine AC on the prognosis of patients with borderline resectable pancreatic cancer is not clear. Methodology: We analyzed the prognosis of patients with pancreatic cancer who underwent curative pancreatoduodenectomy or total pancreatectomy in combination with portal/superior mesenteric vein resection (PVR) [PVR (+) group] or without PVR [PVR(-) group]. Results: MST of the PVR (+) group was significantly shorter than that of the PVR(-) group ( $p=0.017$ ). In contrast, when we focused on the patients with gemcitabine AC, there was no significant difference in MST between the PVR (+) and the PVR (-) groups ( $p=0.247$ ). Furthermore, we compared MST of two subgroups in the PVR (+) group depending on gemcitabine AC status. In the PVR (+) group, MST of the patients with gemcitabine AC was significantly longer than that without gemcitabine AC ( $p=0.003$ ). This was also true for the patients with pancreatic cancer which had histologically proven invasion to portal/superior mesenteric vein (PV/SMV) ( $p=0.001$ ). Conclusions: The prognosis of patients with pancreatic cancer invading PV/SMV can be improved by combination therapy with PVR and gemcitabine adjuvant chemotherapy.

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[527]

**TÍTULO / TITLE:** - Cellular uptake of 9-hydroxypheophorbide-alpha and its photoactivation to induce ER stress-related apoptosis in human cervical cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lasers Med Sci. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1007/s10103-013-1331-](#)

[4](#)

**AUTORES / AUTHORS:** - Ahn JC; Biswas R; Moon JH; Chung PS

**INSTITUCIÓN / INSTITUTION:** - Medical Laser Research Center, College of Medicine, Dankook University, Cheonan, Chungnam, South Korea.

**RESUMEN / SUMMARY:** - The 9-hydroxypheophorbide-alpha (9-HPbD) is a chlorophyll derivative and was found to be very effective for photodynamic therapy of tumor cells. The current study investigates uptake, retention, and intracellular localization of 9-HPbD by HeLa, human cervical cancer cells via fluorescence spectrophotometry and confocal laser scanning microscopy, and its photodynamic effect against human cervical carcinoma cell. HeLa cells exposed to 9-HPbD exhibited a linear uptake of photosensitizer during the first 12 h, and after removal of 9-HPbD, cell fluorescence was observed to decrease gradually over the next 12 h. Cells treated with 9-HPbD and stained with a panel of organelle-specific fluorescence probes (MitoTracker, LysoTracker, and

ER-Tracker) revealed an intracellular fluorescence distribution restricted to cytoplasmic compartments with no detectable fluorescence in the nucleus. The 9-HPbD showed cytotoxicity effect against HeLa cells in 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. Endoplasmic reticulum (ER) disruption and cellular calcium dynamics also showed a photoactivation followed by cell death. The apoptotic effect of 9-HPbD was confirmed by caspase 3 activity study and immunofluorescence study of caspase 12. Morphological observation through the transmission electron microscopy and scanning electron microscopy also confirmed that 9-HPbD can induce apoptosis in HeLa cells. Therefore, it can be concluded that maximum uptake and clearance time of 9-HPbD was 12 h with endoplasmic reticulum as the major organelle site in cellular uptake, and 9-HPbD can induce apoptosis in HeLa cells through ER stress-related pathways via activation of caspase 12.

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[528]

**TÍTULO / TITLE:** - Hybrid liposomes composed of dimyristoylphosphatidylcholine and trehalose surfactants inhibit the growth of tumor cells along with apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biol Pharm Bull. 2013 May 21.

**AUTORES / AUTHORS:** - Matsumoto Y; Cao E; Ueoka R

**INSTITUCIÓN / INSTITUTION:** - Division of Applied Life Science, Graduate School of Engineering, Sojo University.

**RESUMEN / SUMMARY:** - Novel hybrid liposomes (DMTre) composed of L-alpha-dimyristoylphosphatidylcholine (DMPC) and trehalose surfactant were produced and inhibitory effects of DMTre on the growth of human colon carcinoma (HCT116) and gastric carcinoma (MKN45) in vitro were examined. The remarkably high inhibitory effects of DMTre on the growth of HCT116 and MKN45 cells were obtained without affecting the growth of normal cells. The thickness of fixed aqueous layer of DMTre was larger than that of DMPC liposomes and increased in a dose-dependent manner. The induction of apoptosis by DMTre was revealed on the basis of flow cytometric analysis. DMTre induced apoptosis through the activation of caspases and mitochondria via Bax. It is noteworthy that remarkable inhibitory effects of DMTre on the growth of human colon and gastric carcinoma cells leading to apoptosis were obtained for the first time.

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[529]

**TÍTULO / TITLE:** - MicroRNAs as prognostic markers in indolent primary cutaneous B-cell lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mod Pathol. 2013 Apr;26(4):617. doi: 10.1038/modpathol.2012.209.

- Enlace al texto completo (gratis o de pago)

[1038/modpathol.2012.209](#)

**AUTORES / AUTHORS:** - Monsalvez V; Montes-Moreno S; Artiga MJ; Rodriguez ME; Espiridion BS; Lozano M; Fernandez-de-Misa R; Rodriguez-Peralto JL; Piris MA; Ortiz-Romero PL

[530]

**TÍTULO / TITLE:** - A common gene variant in PLS3 predicts colon cancer recurrence in women.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 3.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-0754-](#)

[7](#)

**AUTORES / AUTHORS:** - Szkandera J; Winder T; Stotz M; Weissmueller M; Langsenlehner T; Pichler M; Samonigg H; Renner W; Gerger A; Absenger G

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Graz, Austria.

**RESUMEN / SUMMARY:** - Recent evidence suggests that PLS3 (T-Plastin), an important member of the actin filamentous network, significantly influences cell invasion and metastasis. Germline polymorphisms within the PLS3 gene may impact the gene's function, resulting in inter-individual differences in tumor recurrence capacity. In the present study, we investigated the association of germline polymorphisms in PLS3 to predict time to recurrence (TTR) in patients with stage II and III colon cancer. A total of 264 patients with histologically confirmed colon cancer were included in this retrospective study. Germline DNA was genotyped for rs871773 C>T, rs757124 C>G, rs1557770 G>T, rs6643869 G>A, and rs2522188 C>T in the PLS3 gene by 5'-exonuclease (TaqMan) technology. As the PLS3 gene is located on the X chromosome, a gender-specific statistical analysis was performed. In univariate analysis, the minor allele of PLS3 rs871773 C>T was significantly associated with decreased TTR in women (hazard ratio (HR) = 5.02; 95 % confidence interval (CI) = 1.251-20.114; p = 0.023) and remained significantly associated in multivariate analysis (HR = 6.165; 95 % CI = 1.538-24.716; p = 0.010). Female patients carrying the C/T genotype in PLS3 rs871773 showed a median TTR of 69 months. In contrast, female patients with homozygous C/C had a median TTR of 112 months. There were no significant associations between PLS3 rs871773 C>T and TTR in male and between the other polymorphisms and TTR in male or female colon cancer patients. In conclusion, we identified a common gene variant in PLS3 as an independent prognostic marker in female patients with stage II and III colon cancer. Larger prospective trials are warranted to confirm these findings.

[531]

**TÍTULO / TITLE:** - Microdialysis measurement of intratumoral temozolomide concentration after cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, in a U87 glioma model.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2172-](#)

[3](#)

**AUTORES / AUTHORS:** - Grossman R; Tyler B; Rudek MA; Kim E; Zadnik P; Khan U; Blakeley JO; Pathak AP; Brem H

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Johns Hopkins University School of Medicine Baltimore, 1550 Orleans Street/Cancer Research Building II Room 2M45, Baltimore, MD, 21231, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Combining anti-angiogenesis agents with cytotoxic agents for the treatment of malignant gliomas may affect the cytotoxic drug distribution by normalizing the blood-brain barrier (BBB). This study examines the intratumoral concentration of temozolomide (TMZ) in the presence and absence of the pan-VEGF receptor tyrosine kinase inhibitor, cediranib. METHODS: Seven nude rats bearing U87 intracerebral gliomas had a microdialysis probe centered within the tumor. Ten-days after tumor implantation, TMZ (50 mg/kg) was given orally. The extracellular fluid (ECF) concentrations of TMZ within the tumor were assessed via microdialysis for 6 h following TMZ administration. Cediranib (6 mg/kg) was then given orally, and 12 h later, TMZ was re-administered with subsequent microdialysis collection. A subset of animals also underwent functional MRI to assess angiogenesis in vivo at post-inoculation days 12 and 21, before and after the cediranib treatment. RESULTS: After dosing of oral TMZ only, ECF-TMZ mean-C max and area under the concentration curve(AUC<sub>0-infinity</sub>) within the tumor were 0.59 mug/mL and 1.82 mug h/mL, respectively. Post-cediranib, ECF-TMZ mean-C max and AUC<sub>0-infinity</sub> were 0.83 mug/mL and 3.72 +/- 0.61 mug h/mL within the tumor, respectively. This represented a 1.4-fold (p = 0.3) and 2.0-fold (p = 0.06) increase in the ECF-TMZ C max and AUC<sub>0-infinity</sub>, respectively, after cediranib administration. In vivo MRI measurements of the various vascular parameters were consistent with a BBB "normalization" profile following cediranib treatment. CONCLUSIONS: In the U87 intracerebral glioma model, within the first day of administration of cediranib, the intratumoral concentrations of TMZ in tumor ECF were slightly, but not statistically significantly, increased when compared to the treatment of TMZ alone with radiographic evidence of a normalized BBB.

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[532]

**TÍTULO / TITLE:** - Brassinin Induces Apoptosis in PC-3 Human Prostate Cancer Cells through the Suppression of PI3K/Akt/mTOR/S6K1 Signaling Cascades.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Phytother Res. 2013 May 20. doi: 10.1002/ptr.5010.

●●Enlace al texto completo (gratis o de pago) [1002/ptr.5010](#)

**AUTORES / AUTHORS:** - Kim SM; Park JH; Kim KD; Nam D; Shim BS; Kim SH; Ahn KS; Choi SH; Ahn KS

**INSTITUCIÓN / INSTITUTION:** - College of Korean Medicine, Kyung Hee University, 1 Hoegi-Dong Dongdaemun-Gu, Seoul, 130-701, Republic of Korea.

**RESUMEN / SUMMARY:** - The oncogenic PI3K/Akt/mammalian target of rapamycin (mTOR) signaling axis and its downstream effector, the ribosomal protein S6 kinase 1 (S6K1) play a key role in mediating cell survival in various tumor cells. Here, we investigated the effects of brassinin (BSN), a phytoalexin first identified as a constituent of cabbage, on the PI3K/Akt/mTOR/S6K1 activation, cellular proliferation, and apoptosis in PC-3 human prostate cancer. BSN exerted a significant dose-dependent cytotoxicity and reduced constitutive phosphorylation of Akt against androgen-independent PC-3 cells as compared to androgen-dependent LNCaP cells. Moreover, knockdown of androgen receptor (AR) by small interfering RNA enhanced the potential effect of BSN on induction of apoptosis in LNCaP cells. BSN clearly suppressed the constitutive activation of PI3K/Akt/mTOR/S6K1 signaling cascade, which correlated with the induction of apoptosis as characterized by accumulation of cells in subG1 phase, positive Annexin V binding, TUNEL staining, loss of mitochondrial membrane potential, down-regulation of antiapoptotic and proliferative proteins, activation of caspase-3, and cleavage of PARP. Additionally, BSN could block broad-spectrum inhibition of PI3K/Akt/mTOR/S6K1 axes, and aberrant Akt activation by pcDNA3-myr-HA-Akt1 plasmid could not prevent the observed suppressive effect of BSN on constitutive mTOR activation. Finally, overexpression of Bcl-2 also attenuated BSN-mediated apoptosis in PC-3 cells. Taken together, our findings suggest that BSN can interfere with multiple signaling cascades involved in tumorigenesis and might be provided as a potential therapeutic candidate for both the prevention and treatment of prostate cancer. Copyright © 2013 John Wiley & Sons, Ltd.

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[533]

**TÍTULO / TITLE:** - Initiation of apoptosis, cell cycle arrest and autophagy of esophageal cancer cells by dihydroartemisinin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Jun;67(5):417-24. doi: 10.1016/j.biopha.2013.01.013. Epub 2013 Feb 19.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2013.01.013](#)

**AUTORES / AUTHORS:** - Du XX; Li YJ; Wu CL; Zhou JH; Han Y; Sui H; Wei XL; Liu L; Huang P; Yuan HH; Zhang TT; Zhang WJ; Xie R; Lang XH; Jia DX; Bai YX

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Oncology, The Third Affiliated Hospital, Harbin Medical University, Harbin, 150, Haping St, Nangang District, Harbin, 150081, People's Republic of China.

**RESUMEN / SUMMARY:** - Dihydroartemisinin (DHA) has recently been shown anti-tumor activity in various cancer cells. However, its effect on esophageal cancer remains unclear. In this study, for the first time, we demonstrated that DHA reduced viability of esophageal cancer cells in a dose-dependent manner. The mechanism was at least partially due to DHA induced apoptosis by upregulating the expression of Bax, downregulating Bcl-2, Bcl-xL and Procaspase-3, and increasing caspase-9 activation, induced cell cycle arrest by downregulating cyclin E, CDK2 and CDK4. Furthermore, we firstly found that DHA induced autophagy in cancer cells. We concluded DHA might be a novel agent against esophageal cancer.

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[534]

**TÍTULO / TITLE:** - Prognostic value of epidermal growth factor receptor, p53 and galectin-3 expression in papillary thyroid carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Int Med Res. 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago)

[1177/0300060513477312](http://1177/0300060513477312)

**AUTORES / AUTHORS:** - Lee YM; Lee JB

**INSTITUCIÓN / INSTITUTION:** - Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** The aim of this study was to determine the protein expression and prognostic value of epidermal growth factor receptor (EGFR), p53 and galectin-3 in papillary thyroid carcinoma (PTC). **METHODS:** A retrospective analysis was performed using tumour specimens from patients with PTC who underwent thyroidectomy between July 2007 and December 2008. The percentages of tumour cells staining positively for EGFR, galectin-3 and p53 were determined by immunohistochemistry. Associations between protein expression and age, sex, extrathyroidal extension and lymph node metastasis were assessed, together with the total Metastasis, Age, Completeness of resection, Invasion, Size (MACIS) score (a marker of prognosis). MACIS prognostic scores were categorized into four groups. **RESULTS:** Data from 168 patients with PTC (mean follow-up, 35 months) were included. EGFR expression was significantly associated with male sex and lymph node metastasis; p53 expression was higher in males than in females; galectin-3 expression was not significantly associated with age, sex, extrathyroidal extension, lymph node metastasis or total MACIS score category, however. **CONCLUSION:** Immunohistochemical evaluation of EGFR and p53

expression in patients with PTC may be useful for determining prognosis, in PTC patients.

[535]

**TÍTULO / TITLE:** - Concurrent inhibition of PI3K and mTORC1/mTORC2 overcomes resistance to rapamycin induced apoptosis by down-regulation of Mcl-1 in mantle cell lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Apr 12. doi: 10.1002/ijc.28206.

●●Enlace al texto completo (gratis o de pago) [1002/ijc.28206](#)

**AUTORES / AUTHORS:** - Muller A; Zang C; Chumduri C; Dorken B; Daniel PT; Scholz CW

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Oncology and Tumor Immunology, University Medical Center Charite, Campus Berlin-Buch, Humboldt University Berlin, Germany; Clinical and Molecular Oncology, Max Delbrück Center for Molecular Medicine, 13125 Berlin-Buch, Germany.

**RESUMEN / SUMMARY:** - Mantle cell lymphoma (MCL) is an aggressive form of Non-Hodgkin-Lymphoma (NHL) with an ongoing need for novel treatments. Apart from the translocation t(11;14), which facilitates constitutive transcription of cyclin D1, additional aberrations are frequently observed in MCL, including a recurrent dysregulation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway. mTOR, a key component of this pathway, is pivotal for the assembly of mTOR complex (mTORC) 1 and 2. Temsirolimus an analog of the mTOR inhibitor rapamycin is approved for the treatment of relapsed MCL. Response rates, however, are low and response durations are short. We demonstrate that inhibition of mTORC1 by rapamycin or blocking of mTORC1 and mTORC2 in conjunction with PI3K by NVP-BEZ235 reduces proliferation of MCL cell lines to a similar extent. However, only NVP-BEZ235 is able to sufficiently inhibit the downstream pathway of mTOR and to mediate cell death through activation of the intrinsic apoptosis pathway. Further analysis demonstrated that the anti-apoptotic Bcl-2 family member Mcl-1 plays a central role in regulation of MCL survival. While Mcl-1 protein levels remained unchanged after co-culture with rapamycin, they were down-regulated in NVP-BEZ235 treated cells. Furthermore, inhibition of Mcl-1 by the BH3-only mimetic obatoclax or down-regulation of constitutive Mcl-1, but not of Bcl-2 or Bcl-xL, by siRNA facilitated cell death of MCL cells and enhanced rapamycin's as well as NVP-BEZ235's capacity to induce cell death. Our findings may help to lay the foundation for further improvements in the treatment of MCL. © 2013 Wiley Periodicals, Inc.

[536]

**TÍTULO / TITLE:** - Chemosensitivity induced by down-regulation of microRNA-21 in gemcitabine-resistant pancreatic cancer cells by indole-3-carbinol.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1473-81.

**AUTORES / AUTHORS:** - Paik WH; Kim HR; Park JK; Song BJ; Lee SH; Hwang JH

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea.

**RESUMEN / SUMMARY:** - BACKGROUND/AIM: Overexpression of microRNA-21 (miR-21) indicates chemoresistance in pancreatic cancer. We evaluated the change of chemosensitivity to gemcitabine through the down-regulation of miR-21 in human pancreatic cancer cells (Panc-1). MATERIALS AND METHODS: The efficacy of indole-3-carbinol (I3C) in suppressing miR-21 expression and its anticancer effect in combination with gemcitabine were investigated.

RESULTS: Down-regulation of miR-21 by I3C was positively-correlated in a time- and dose-dependent manner. I3C and gemcitabine combination therapy increased cytotoxicity in Panc-1 cells. Transfection of miR-21 mimic abrogated I3C-induced sensitivity to gemcitabine. DNA fragmentation and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assays showed that pre-treatment with I3C enhanced apoptosis and this effect was attenuated by miR-21 transfection. The expression of programmed cell death-4 (PDCD4) was increased by I3C and reduced by miR-21 transfection.

CONCLUSION: I3C would be effective for enhancing sensitivity of pancreatic cancer cells to gemcitabine via down-regulation of miR-21. Such enhanced chemosensitivity might be explained by the increased expression of PDCD4, which is a downstream target which miR-21 negatively regulates.

[537]

**TÍTULO / TITLE:** - Postmenopausal breast cancer, androgens, and aromatase inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 May;139(1):1-11. doi: 10.1007/s10549-013-2505-2. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2505-](#)

[2](#)

**AUTORES / AUTHORS:** - Campagnoli C; Pasanisi P; Castellano I; Abba C; Brucato T; Berrino F

**INSTITUCIÓN / INSTITUTION:** - Unit of Endocrinological Gynecology, Ospedale Ginecologico Sant'Anna di Torino, Turin, Italy.

**RESUMEN / SUMMARY:** - Recent data can help to better define the long debated relationship between androgens and breast cancer (BC) after menopause. We reviewed the available literature data on: the origin of androgens after menopause, the association between circulating androgens and BC incidence

and recurrence, the relationship between circulating and intratumoral hormones, the prognostic significance of the presence of androgen receptors (ARs) in the different BC subtypes, the androgen effect on BC cell lines, and the relationship between androgens and aromatase inhibitors. Epidemiological, clinical, and preclinical data on the role of androgens and of ARs on estrogen receptor (ER)-negative BC are somewhat controversial. However, most preclinical studies suggest that activated ARs, when present, have a proliferative effect, particularly in HER2 expressing cell lines, due to the cross-talk between AR and HER2 pathways. As regards ER-positive BC, epidemiological studies associate androgen levels with increased incidence and risk of recurrences, whilst clinical studies associate the AR positivity with a better prognosis. Preclinical studies suggest that the action of androgens is bidirectional: mainly proliferative, because circulating androgens are the precursors of estrogens, but also anti-proliferative, because AR activation restrains ER activity. The relative increase of androgenic action that follows the blocking of androgen aromatization into estrogens by aromatase inhibitors (AIs), could contribute to their therapeutic efficacy in AR-positive cases. Available data, although defining a complex picture, suggest that circulating androgen levels are clinically relevant, particularly when AIs are used.

[538]

**TÍTULO / TITLE:** - Apoptosis inducing activity of benzophenanthridine-type alkaloids and 2-arylbenzofuran neolignans in HCT116 colon carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Phytomedicine. 2013 Apr 30. pii: S0944-7113(13)00135-9. doi: 10.1016/j.phymed.2013.03.026.

●●Enlace al texto completo (gratis o de pago)

[1016/j.phymed.2013.03.026](#)

**AUTORES / AUTHORS:** - Mansoor TA; Borralho PM; Luo X; Mulhovo S; Rodrigues CM; Ferreira MJ

**INSTITUCIÓN / INSTITUTION:** - Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal; Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal.

**RESUMEN / SUMMARY:** - Thirteen compounds belonging to different classes of alkaloids (1-9) and lignans (10-13), isolated from the methanol extract of roots of the African medicinal plant *Zanthoxylum capense*, were assayed for their ability as apoptosis inducers in HCT116 colon carcinoma cells. The cytotoxicity of these compounds was evaluated in HCT116 colon carcinoma cells by the MTS assay. Out of the tested compounds, three benzophenanthridine alkaloids (1, 4, and 7), a dibenzyl butyrolactone lignan (10), and two 2-arylbenzofuran neolignans (12 and 13) displayed significant cytotoxicity to HCT116 cells,

confirmed by the Guava ViaCount viability assay. The selected compounds (1, 4, 7, 10, 12, and 13) were further tested for apoptosis induction activity in HCT116 cells, by evaluation of nuclear morphology following Hoechst staining, and by caspase-3 like activity assays. Morphologic evaluation of HCT116 nuclei following Hoechst staining and fluorescence microscopy revealed that compounds 1, 4, 7, 10, 12, and 13 induced apoptosis in HCT116 colon carcinoma cells, producing similar, or higher, apoptosis levels when compared with 5-fluorouracil (5-FU), the cornerstone cytotoxic used in colon cancer treatment for several decades. In fact, HCT116 cells developed morphological changes characteristic of apoptosis, including chromatin condensation, nuclear fragmentation and formation of apoptotic bodies. Importantly, compounds 4 and 13 at 20µM were the most promising in this study, inducing respectively ~11- and 7-fold increases in apoptotic cells as compared to vehicle control, whereas 5-FU increased apoptosis by ~2-fold. Apoptosis induction for compounds 4 and 13 was further confirmed by caspase-3-like activity assays, which showed respectively ~2- and 1.5-fold increases in caspase-3-like activity compared to vehicle control. These results suggested that specific benzophenanthridine alkaloids and 2-arylbenzofuran neolignans isolated from *Zanthoxylum capense* show strong anticancer activity in HCT116 colon carcinoma cells.

[539]

**TÍTULO / TITLE:** - Association between main Caspase Gene Polymorphisms and the Susceptibility and Prognosis of Colorectal Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):565. doi: 10.1007/s12032-013-0565-0. Epub 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0565-](#)

[0](#)

**AUTORES / AUTHORS:** - Wu Z; Li Y; Li S; Zhu L; Li G; Yu Z; Zhao X; Ge J; Cui B; Dong X; Tian S; Hu F; Zhao Y

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology, Public Health College, Harbin Medical University, 157, Baojian Street, Nangang District, Harbin, Heilongjiang Province, People's Republic of China.

**RESUMEN / SUMMARY:** - Caspase (CASP) 3, 8, 9 are important caspases in the apoptosis pathway and play important roles in development and progression of cancer. A case-control study with 451 colorectal cancer (CRC) patients and 631 cancer-free controls were carried out, and CRC patients followed up, to investigate the associations between three main polymorphisms and colorectal cancer risk and prognosis, and their potential interactions with environmental factors on CRC risk among Chinese people. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism and polymerase chain reaction-single strand conformation polymorphism

sequencing. Odds ratio (OR), hazard ratio (HR) and their 95 % confidence intervals (CIs) were estimated with unconditional logistic-regression and Cox proportion hazard model. Individuals harboring the CASP8 -652 6N ins/del plus del/del genotype had a slightly lower risk for CRC compared those with ins/ins genotype (adjusted OR = 0.77, 95 % CI 0.59-0.99, P = 0.04). Significant associations between CASP3 -928 GG genotype and CASP9 -1263 GG genotype and reduced risk of rectal cancer were observed (adjusted OR = 0.56, 95 % CI 0.34-0.92, P = 0.02; adjusted OR = 0.59, 95 % CI 0.36-0.95, P = 0.03, respectively). There was a marginal significant association between CASP8 -652 6N ins/del polymorphism and CRC prognosis (ins/del versus ins/ins, adjusted HR = 0.69, 95 % CI 0.48-0.99, P = 0.04). These findings suggested these polymorphisms and their combinations with dietary factors may be associated with the development of CRC. CASP8 -652 6N ins/del polymorphism may be an independent survival predictor for CRC.

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[540]

**TÍTULO / TITLE:** - Comparison of Antitumor Effects of Native and Recombinant Human Interferon-alpha on Non-small Cell Lung Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):2043-6.

**AUTORES / AUTHORS:** - Santak G; Santak M; Forcic D

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, County Hospital PoZega, Osjecka 107, HR-34 000 PoZega, Croatia. [gsantak@hotmail.com](mailto:gsantak@hotmail.com).

**RESUMEN / SUMMARY:** - BACKGROUND: In the present work, we compared the antitumor effects of native human interferon-alpha (IFN-alpha) (nHuIFN-alpha) and recombinant human IFN-alpha (rHuIFN-alpha) on human lung adenocarcinoma A549 cells. MATERIALS AND METHODS: The antitumor activity was determined by measuring cell viability and apoptosis, while the abundance of mRNA, measured by polymerase chain reaction (PCR), determined the potential role of p21 and survivin in antitumor activity of nHuIFN-alpha. RESULTS: The results show that nHuIFN-alpha significantly reduced A549 cell viability, compared to rHuIFN-alpha. The most potent effect of nHuIFN-alpha was also observed when apoptosis was measured. A549 cells treated with nHuIFN-alpha expressed a significantly higher amount of p21 mRNA, while the amount of survivin mRNA was significantly reduced. CONCLUSION: Considering both the anti-proliferative and anti-apoptotic effects of each IFN-alpha, we conclude that further elucidation of the mechanisms of the antitumor activity of nHuIFN-alpha will help in producing more effective and less toxic therapeutic protocols and preparations.

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[541]

**TÍTULO / TITLE:** - Plasma thrombin-activatable fibrinolysis inhibitor levels and its Thr325Ile polymorphism in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood Coagul Fibrinolysis. 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago)

[1097/MBC.0b013e3283610381](https://doi.org/10.1097/MBC.0b013e3283610381)

**AUTORES / AUTHORS:** - Chengwei X; Xiaoli M; Yuan Z; Li P; Shengjiang W; Chao Y; Yunshan W

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Laboratory Medicine, the Second Hospital of Shandong University bMedical Research & Laboratory Diagnostic Center, Jinan Central Hospital Affiliated to Shandong University cDepartment of Evidence-based Medicine, the Second Hospital of Shandong University, Jinan, China \*Xu Chengwei and Ma Xiaoli contributed equally to this work.

**RESUMEN / SUMMARY:** - Impairment of fibrinolytic function plays an important role in the mechanism of thrombotic disorders in cancer patients. Thrombin-activatable fibrinolysis inhibitor (TAFI) has an antifibrinolytic effect as it can remove partially degraded fibrin C-terminal lysine residues and reduce plasmin formation. The purpose of this study was to investigate whether blood TAFI levels and TAFI Thr325Ile polymorphism could be a risk marker of breast cancer. The plasma TAFI antigen (Ag) level was determined using ELISA assay in 256 patients with breast cancer and 192 healthy controls. TAFI Thr325Ile (rs1926447) polymorphism was genotyped in both patients and control groups using PCR-restriction fragment length polymorphism (PCR-RFLP) and sequencing. The results showed that TAFI Ag levels were significantly higher in breast cancer patients than those in controls (100.6 +/- 15.2 and 82.7 +/- 11.2%,  $P < 0.001$ ). TAFI Ag levels were correlated with metastasis of breast cancer ( $P < 0.001$ ). The Thr/Ile (CT) and Ile/Ile (TT) genotypes were found more frequently in patients group compared with the control group [odds ratio (OR) 2.106; (95% confidence interval, CI 1.379-3.217);  $P < 0.001$ ]. The high-risk T alleles frequency was also higher in patients compared with healthy controls [OR 1.718; (95% CI 1.316-2.243);  $P < 0.001$ ]. The polymorphism was significantly correlated with TAFI Ag levels in either group ( $P < 0.001$ ). The Ile/Ile (TT) genotype had the lowest TAFI Ag level, whereas the Thr/Thr (CC) had the highest one. In conclusion, the plasma TAFI levels and TAFI Thr325Ile genotypes were associated with breast cancer patients in Chinese Han populations and could be considered as the risk indicators of breast cancer.

[542]

**TÍTULO / TITLE:** - Annexin A3 is associated with a poor prognosis in breast cancer and participates in the modulation of apoptosis in vitro by affecting the Bcl-2/Bax balance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Mol Pathol. 2013 Apr 28;95(1):23-31. doi: 10.1016/j.yexmp.2013.04.002.

●●Enlace al texto completo (gratis o de pago)

[1016/j.yexmp.2013.04.002](http://1016/j.yexmp.2013.04.002)

**AUTORES / AUTHORS:** - Zeng C; Ke Z; Song Y; Yao Y; Hu X; Zhang M; Li H; Yin J

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Guangdong Medical College, Dongguan, China. Electronic address: [zengchaosysu@yahoo.com.cn](mailto:zengchaosysu@yahoo.com.cn).

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Annexins are a family of intracellular proteins that bind membrane phospholipids in a Ca<sup>2+</sup> concentration-dependent manner. Several annexins play important roles during tumor progression. However, little is known about the clinical implications and biological functions of Annexin A3 in breast cancer. **METHODS:** Using immunohistochemistry, we analyzed 60 breast cancers for the levels of annexin A3 and investigated the correlation of its expression change with patient's survival via Kaplan-Meier survival analysis. Furthermore, via knockdown of Annexin A3 expression in breast cancer cells with special siRNA, the role of Annexin A3 in the proliferation and apoptosis of breast cancer cells was examined. **RESULTS:** Annexin A3 was expressed at higher level in breast cancer than that in normal breast tissue. The expression of Annexin A3 in human breast carcinoma closely correlated with tumor size and axillary lymph node metastasis. Kaplan-Meier survival analysis revealed a significant inverse correlation between strong Annexin A3 expression and overall patient survival. Moreover, Annexin A3 overexpression was inversely associated with Bax staining and the apoptosis index. Annexin A3 small interfering RNA in MCF-7 and MDA-MB-435 could inhibit cell proliferation, decrease Bcl-2 mRNA and protein expression, and increase Bax mRNA and protein expression. **CONCLUSION:** Our findings indicated that Annexin A3 might be a novel and potential prognostic marker for patients with breast cancer and be involved in regulating apoptosis by affecting Bcl-2/Bax balance.

[543]

**TÍTULO / TITLE:** - Cytotoxicity and apoptosis induction in human breast adenocarcinoma MCF-7 cells by (+)-cyanidan-3-ol.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Toxicol Pathol. 2013 May 21. pii: S0940-2993(13)00057-2. doi: 10.1016/j.etp.2013.04.005.

●●Enlace al texto completo (gratis o de pago) [1016/j.etp.2013.04.005](http://1016/j.etp.2013.04.005)

**AUTORES / AUTHORS:** - Monga J; Pandit S; Chauhan CS; Sharma M

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, Jaypee University of Information Technology, Wagnaghat, Himachal Pradesh, India.

**RESUMEN / SUMMARY:** - The objective of this study was to evaluate the cytotoxicity and possible signalling pathway implicated in (+)-cyanidan-3-ol (CD-

3) induced apoptosis in the human breast adenocarcinoma cell line (MCF-7). The effects of CD-3 on cell proliferation of MCF-7 cells were evaluated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT), sulforhodamine B (SRB) and lactate dehydrogenase (LDH) assays. Cell apoptosis was detected by Hoechst 33258 (HO) and acridine orange/ethylene dibromide (AO/EB) staining and DNA fragmentation analysis. The expressions of apoptosis-related genes were assessed by RT-PCR and ELISA. Our data revealed that CD-3 induced MCF-7 cell death in a dose-dependent manner. Marked changes in apoptotic morphology was clearly observed after CD-3 treatment. CD-3 induced cell death was considered to be apoptotic by observing the typical apoptotic morphological change under fluorescent microscopy and DNA fragmentation assays. The induction of apoptosis is correlated with the increased mRNA expressions of p53, Bax, and caspase-3, -7, -8 and -9 and decreased mRNA expressions of bcl-2. Subsequently, CD-3 decreased the mRNA expressions of mdm2, p65, c-jun, c-fos in MCF-7 cells. The protein levels of p53, Bax, and caspase-3 were increased, whereas, that of p65, c-jun and Bcl-2 were decreased in MCF-7 cells on CD-3 treatment. These results clearly demonstrated that CD-3 effectively induced growth inhibition and apoptosis in MCF-7 cells.

[544]

**TÍTULO / TITLE:** - Phase II study on lapatinib in advanced EGFR-positive chordoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1093/annonc/mdt117](#)

**AUTORES / AUTHORS:** - Stacchiotti S; Tamborini E; Lo Vullo S; Bozzi F; Messina A; Morosi C; Casale A; Crippa F; Conca E; Negri T; Palassini E; Marrari A; Palmerini E; Mariani L; Gronchi A; Pilotti S; Casali PG

**INSTITUCIÓN / INSTITUTION:** - Sarcoma Unit, Departments of Cancer Medicine.

**RESUMEN / SUMMARY:** - BACKGROUND: To report on a prospective, investigator-driven, phase II study on lapatinib in epidermal growth factor receptor (EGFR)-positive advanced chordoma patients. PATIENTS AND METHODS: From December 2009 to January 2012, 18 advanced progressing chordoma patients entered this study (median age: 61 years; disease extent: metastatic 72% and locally advanced 28%). Epidermal growth factor receptor (EGFR) expression and activation were evaluated by immunohistochemistry and/or phospho-arrays, real-time polymerase chain reaction, fluorescence immunostaining. Fluorescence in situ hybridization analysis was also carried out. Patients received lapatinib 1500 mg/day (mean dose intensity = 1282 mg/day), until progression or toxicity. The primary study end point was response rate (RR) as per Choi criteria. Secondary end points were RR by Response Evaluation Criteria in Solid Tumor (RECIST), overall survival, progression-free

survival (PFS) and clinical benefit rate (CBR; RECIST complete response + partial response (PR) + stable disease (SD)  $\geq$  6 months). RESULTS: All patients were evaluable for response. Six (33.3%) patients had PR and 7 (38.9%) SD, as their best Choi responses, corresponding to RECIST SD in all cases. Median PFS by Choi was 6 [interquartile (IQ) range 3-8] months. Median PFS by RECIST was 8 (IQ range 4-12) months, with a 22% CBR. CONCLUSIONS: This phase II study showed a modest antitumor activity of lapatinib in chordoma. The clinical exploitation of EGFR targeting in chordoma needs to be further investigated, both clinically and preclinically. Clinical trial Registration No: EU Clinical Trials Register trial no. 2009-014456-29.

[545]

**TÍTULO / TITLE:** - Prognostic parameters for acute esophagus toxicity in Intensity Modulated Radiotherapy and concurrent chemotherapy for locally advanced non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Radiother Oncol. 2013 May 3. pii: S0167-8140(13)00187-4. doi: 10.1016/j.radonc.2013.04.012.

●●Enlace al texto completo (gratis o de pago)

[1016/j.radonc.2013.04.012](#)

**AUTORES / AUTHORS:** - Uyterlinde W; Chen C; Kwint M; de Bois J; Vincent A; Sonke JJ; Belderbos J; van den Heuvel M

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Oncology, NKI-AVL, Amsterdam, The Netherlands. Electronic address: [w.uyterlinde@nki.nl](mailto:w.uyterlinde@nki.nl).

**RESUMEN / SUMMARY:** - BACKGROUND AND PURPOSE: The aim of this study was to correlate clinical and dosimetric variables with acute esophageal toxicity (AET) following Intensity Modulated Radiotherapy (IMRT) with concurrent chemotherapy for locally advanced non-small cell lung cancer (NSCLC). In addition, timeline of AET was reported. MATERIAL AND METHODS: 153 patients with locally advanced NSCLC treated with 66Gy/2.75Gy/24 fractions of radiotherapy and concurrent daily low dose cisplatin were selected. Medical records and treatments of these patients were retrospectively reviewed. Maximum AET grade 2 and maximum grade 3 were the endpoints of this study. Dates for onset, maximum and recovery (to baseline) of AET were reported. Univariate and multivariate analysis were applied to correlate clinical, tumor, dosimetric and chemotherapy dose variables to AET grade 2 and grade 3. RESULTS: AET grade 2 occurred in 37% and grade 3 in 20% of the patients. The median onset of AET was around day 15 for all grades. The median onset of the maximum grade was day 30 for both grades 2 and 3. The median duration was 43days for grade 1, 50days for grade 2 and >80days for grade 3. Of the grade 3 AET patients, 48% recovered within 3months. Esophagus V50, ethnic background, and the number of cisplatin administrations were significantly correlated with grade 3 AET. CONCLUSIONS: For NSCLC patients

treated with concurrent chemotherapy and IMRT A higher number of cisplatin administrations, non-Caucasian background and higher V50oes were associated with grade 3 AET. The median onset of AET grade 3 is 15days after the start of treatment, maximized at day 30, with a median duration of >80days.

[546]

**TÍTULO / TITLE:** - Cytomorphological Factors and BRAF Mutation Predicting Risk of Lymph Node Metastasis in Preoperative Liquid-Based Fine Needle Aspirations of Papillary Thyroid Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Cytol. 2013;57(3):252-8. doi: 10.1159/000343617. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1159/000343617](#)

**AUTORES / AUTHORS:** - Chung SY; Lee JS; Lee H; Park SH; Kim SJ; Ryu HS

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Cancer Center, Dongnam Institute of Radiological and Medical Sciences, Busan, South Korea.

**RESUMEN / SUMMARY:** - Objective: Preoperative fine needle aspiration biopsy (FNAB) has become the initial diagnostic method for papillary thyroid carcinoma (PTC). Identification of cytomorphologic factors predicting lymph node metastasis (LNM) is clinically important for determining the appropriate treatment regimen due to the high rate of lymph node involvement in PTC at the time of diagnosis. Hobnail features (HF) have previously been described as potential histomorphologic features in the histological examination of PTC. This study evaluated the value of HF as a predictor of LNM. Study Design: Histologically confirmed FNABs (n = 111) of papillary thyroid microcarcinoma prepared by the liquid-based method were enrolled. Along with other cytomorphologic parameters, HF were evaluated for their value in predicting LNM. Results: Although HF were closely correlated with cytoplasmic vacuoles of tumor cells and background macrophages (p < 0.05), which were considered diagnostic indicators of PTC with cystic changes, HF were only found to be significantly correlated with LNM (p = 0.008). The BRAF(V660E) mutation was not associated with LNM. All combinations including HF were revealed as stronger predictors of LNM (odds ratios: 2.254-2.524, p < 0.05). Conclusions: HF, a distinctive cytomorphologic feature, may be used as a factor predicting LNM in preoperative FNAB of PTC.

[547]

**TÍTULO / TITLE:** - Bortezomib induces apoptosis of endometrial cancer cells through microRNA-17-5p by targeting p21.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Biol Int. 2013 May 28. doi: 10.1002/cbin.10139.

●●Enlace al texto completo (gratis o de pago) [1002/cbin.10139](#)

**AUTORES / AUTHORS:** - Shen Y; Lu L; Xu J; Meng W; Qing Y; Liu Y; Zhang B; Hu H

**INSTITUCIÓN / INSTITUTION:** - Gynecology and Obstetrics Department of the First Affiliated Hospital of JiNan Medical University, Guangzhou, 510360.

**RESUMEN / SUMMARY:** - Bortezomib suppresses ubiquitin (Ub)-dependent protein degradation and preferentially kills various tumor cells in vitro and in animal models. However, its mechanism of action is not fully understood. We report that bortezomib inhibits the proliferation and proteasomal activity of human endometrial cancer cells and induces G2/M arrest and apoptosis by modulating the miRNA level. By miRNA microarray, iR-17-5p was the most downregulated of all those in HTB-111 and Ishikawa cells after bortezomib treatment. This observation was confirmed by quantitative real-time PCR (qRT-PCR). Target prediction using TargetScan software identified p21 as a potential target for miR-17-5p, which was confirmed by luciferase reporter, qRT-PCR and Western blot assays. The transfection of miR-17-5p mimics or siRNA-p21 reversed the effect of bortezomib on HTB-111 and Ishikawa cells, indicating that miR-17-5p may mediate the function of bortezomib by targeting p21 in endometrial cancer cells. These findings show novel mechanisms by which bortezomib inhibits proliferation and promotes the apoptosis of human endometrial cancer cells.

[548]

**TÍTULO / TITLE:** - Ghrelin induces apoptosis in colon adenocarcinoma cells via proteasome inhibition and autophagy induction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Apoptosis. 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1007/s10495-013-0856-](#)

[0](#)

**AUTORES / AUTHORS:** - Bonfili L; Cuccioloni M; Cekarini V; Mozzicafreddo M; Palermo FA; Cocci P; Angeletti M; Eleuteri AM

**INSTITUCIÓN / INSTITUTION:** - School of Biosciences and Biotechnology, University of Camerino, Via Gentile III da Varano, 62032, Camerino, Macerata, Italy, [laura.bonfili@unicam.it](mailto:laura.bonfili@unicam.it).

**RESUMEN / SUMMARY:** - Ghrelin is a metabolism-regulating hormone recently investigated for its role in cancer survival and progression. Controversially, ghrelin may act as either anti-apoptotic or pro-apoptotic factor in different cancer cells, suggesting that the effects are cell type dependent. Limited data are currently available on the effects exerted by ghrelin on intracellular proteolytic pathways in cancer. Both the lysosomal and the proteasomal systems are fundamental in cellular proliferation and apoptosis regulation. With the aim of exploring if the proteasome and autophagy may be possible targets of ghrelin in cancer, we exposed human colorectal adenocarcinoma cells to ghrelin. Preliminary in vitro fluorimetric assays evidenced for the first time a

direct inhibition of 20S proteasomes by ghrelin, particularly evident for the trypsin-like activity. Moreover, 1 μM ghrelin induced apoptosis in colorectal adenocarcinoma cells by inhibiting the ubiquitin-proteasome system and by activating autophagy, with p53 having an “interactive” role.

[549]

**TÍTULO / TITLE:** - Influence of CYP2D6-genotype on tamoxifen efficacy in advanced breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Jun;139(2):553-60. doi: 10.1007/s10549-013-2565-3. Epub 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s10549-013-2565-](#)

[3](#)

**AUTORES / AUTHORS:** - Karle J; Bolbrinker J; Vogl S; Kreutz R; Denkert C; Eucker J; Wischnewsky M; Possinger K; Regierer AC

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology and Hematology, Charite-Universitätsmedizin Berlin, Chariteplatz 1, 10117, Berlin, Germany.

**RESUMEN / SUMMARY:** - The influence of CYP2D6 genotype on the efficacy of tamoxifen (Tam) has been extensively analyzed in early breast cancer with conflicting results. However, there is only scarce data regarding this potential influence in advanced breast cancer (ABC). We hypothesize that Tam is more effective in patients with a functional CYP2D6 allele than in patients with impaired CYP2D6 activity. ABC patients with prior or ongoing palliative Tam treatment (20 mg/d) were eligible. Genomic DNA was extracted from blood (n = 51) and formalin-fixed, paraffin-embedded tissue (n = 43). CYP2D6\*2, \*3, \*4, \*5, \*6, \*10, \*17, \*29, \*41, CYP2D6 duplication and multiplication were determined in blood and CYP2D6\*4 in tissue samples. Primary endpoint was progression free survival (PFS); secondary endpoints included clinical benefit (CB), and overall survival (OS). The clinical charts were retrospectively analyzed regarding survival and treatment effects. Genotyping was performed blinded and clinical data were analyzed separately. 94 patients were identified with a median age of 59 years (29-90 years). In 6 patients genotyping did not show conclusive results, therefore these patients were excluded from further analysis. Genotyping results were as follows: 1.1 % ultrarapid, 84.1 % extensive, 3.4 % intermediate, and 11.4 % poor metabolizers. Patients without any fully functional allele (IM/IM, IM/PM, PM/PM) had a significant shorter PFS and OS compared to patients with at least one functional allele (EM/EM, EM/IM, EM/PM) (PFS: p = 0.017; HR = 2.19; 95 % CI 1.15-4.18; OS: p = 0.028; HR = 2.79; 95 % CI 1.12-6.99). The CB rate was 73 % for EM-group and 38.5 % for IM + PM-group (p = 0.019). Our results show a significant influence of the CYP2D6 genotype on the efficacy of Tam in the treatment of ABC. In contrast to the adjuvant setting, the evidence in the palliative setting is congruent. CYP2D6 testing in ABC should be considered.

[550]

**TÍTULO / TITLE:** - Primary cardiac angiosarcoma in a 25-year-old man: excision, adjuvant chemotherapy, and multikinase inhibitor therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tex Heart Inst J. 2013;40(2):186-8.

**AUTORES / AUTHORS:** - Bellitti R; Buonocore M; De Rosa N; Covino FE; Casale B; Sante P

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiovascular Surgery and Transplants (Drs. Bellitti, Casale, and Covino) and Anatomic Pathology and Histology (Dr. De Rosa), Monaldi Hospital; and Department of Cardiothoracic and Respiratory Sciences (Drs. Buonocore and Sante), Second University of Naples; 80131 Naples, Italy.

**RESUMEN / SUMMARY:** - Primary cardiac tumors do not occur frequently, and only one quarter of them, chiefly sarcomas, are malignant. Patients with angiosarcoma typically have a shorter survival time than do patients with other sarcomas, and the prognosis for survival depends strictly on the stage of the disease at the time of diagnosis and the possibility of complete surgical excision. Chemotherapy and radiotherapy have well-established postoperative roles because of the high probability of metastasis. We report the case of a 25-year-old man who presented with pericardial effusion and echocardiographic evidence of an intracavitary right atrial mass but without the bulky, infiltrative growth typical of this location of the disease. Malignancy was suggested by the clinical presentation, the location of the mass in the right side of the heart, and the absence of conditions favoring thrombus formation. After complete surgical excision, the mass was confirmed to be an angiosarcoma. Conventional adjuvant chemotherapy and maintenance therapy with inhibitors of CD117 (c-kit) and vascular endothelial growth factor relieved the patient's clinical symptoms and enabled his long-term, disease-free survival. In addition to reporting this case, we discuss aspects of the diagnosis and treatment of angiosarcoma.

[551]

**TÍTULO / TITLE:** - Interstitial Lung Disease Associated with Gefitinib in Japanese Patients with EGFR-mutated Non-small-cell Lung Cancer: Combined Analysis of Two Phase III Trials (NEJ 002 and WJTOG 3405).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Jpn J Clin Oncol. 2013 Jun;43(6):664-8. doi: 10.1093/jjco/hyt049. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1093/jjco/hyt049](#)

**AUTORES / AUTHORS:** - Akamatsu H; Inoue A; Mitsudomi T; Kobayashi K; Nakagawa K; Mori K; Nukiwa T; Nakanishi Y; Yamamoto N

**INSTITUCIÓN / INSTITUTION:** - \*Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan. [h.akamatsu@scchr.jp](mailto:h.akamatsu@scchr.jp).

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Interstitial lung disease associated with gefitinib is a critical adverse reaction. When gefitinib was administered to EGFR-unknown patients, the interstitial lung disease incidence rate was approximately 3-4% in Japan, and usually occurs during the first 4 weeks of treatment. However, it has not been fully investigated in EGFR-mutated patients. **METHODS:** We collected clinical records of participants of two Phase III trials (WJTOG 3405 and NEJ 002), which compared gefitinib with platinum doublet chemotherapy. All patients were EGFR mutated, chemo-naive and had good performance status. **RESULTS:** A total of 402 patients were enrolled in this study. In the gefitinib arm, 10 (5.0%) of 201 patients developed interstitial lung disease, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed interstitial lung disease (Grade 1) in the chemotherapy arm. With regard to gefitinib, smoking history was significantly associated with developing interstitial lung disease (odds ratio 0.18; 95% confidence interval: 0.05-0.74; P = 0.01). The cumulative incidence rate of interstitial lung disease was similar in the 0-4, 5-8 and 9-12 week time periods. However, between smokers and never-smokers, cumulative incidence rates in the first 4 weeks were significantly different (4.7% versus 0%, P = 0.03). Three of 10 patients developed interstitial lung disease after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively). **CONCLUSIONS:** Among EGFR-mutated patients, the incidence of interstitial lung disease associated with gefitinib was not different from that in previous reports. Smoking history was associated with developing interstitial lung disease, and smokers had a higher incidence rate of interstitial lung disease in the first 4 weeks.

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[552]

**TÍTULO / TITLE:** - Cyclin D1-a prognostic marker in oropharyngeal squamous cell carcinoma that is tightly associated with high-risk human papillomavirus status.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Pathol. 2013 Apr 5. pii: S0046-8177(13)00061-0. doi: 10.1016/j.humpath.2013.01.021.

●●Enlace al texto completo (gratis o de pago)

[1016/j.humpath.2013.01.021](http://1016/j.humpath.2013.01.021)

**AUTORES / AUTHORS:** - Scantlebury JB; Luo J; Thorstad WL; El-Mofty SK; Lewis JS Jr

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology and Immunology, Washington University, St Louis, MO 63110, USA.

**RESUMEN / SUMMARY:** - Human papillomavirus-related oropharyngeal squamous cell carcinoma has a unique biology and improved prognosis. A new focus is to identify prognostic biomarkers specifically in this human

papillomavirus-positive cohort. We analyzed cyclin D1 immunostaining on a tissue microarray of patients with known clinical follow-up and p16 and human papillomavirus status (by E6/E7 RNA in situ hybridization). Cyclin D1 staining was read visually and digitally. Cutoffs of 5%, 10%, and 30% were separately analyzed as was linear intensity data derived from the image analysis. For the 202 tumors, cyclin D1 expression was > 10% in 25.7% (visual) and 35.5% (digital) of the cases. It was > 30% in 15.8% (visual) and 16.5% (digital) of the cases. High cyclin D1 by both methods, cutoffs, and expression intensity was associated with poorer overall, disease-free, and disease-specific survival in univariate analysis. However, low cyclin D1 expression was also tightly associated with human papillomavirus RNA ( $P < 1.0 \times 10^{-18}$  for all cutoffs) and p16 positivity ( $P < 1.0 \times 10^{-14}$  for all cutoffs). In multivariate analysis using the digital 30% cutoff (the strongest cyclin D1 assessment method), only T stage, p16 status, smoking, and treatment approach associated with survival. Intensity of cyclin D1 expression did, however, significantly substratify the human papillomavirus RNA-positive patients into prognostic subgroups independent of other variables. In summary, cyclin D1 overexpression correlates strongly with patient survival in oropharyngeal squamous cell carcinoma, but its relationship with human papillomavirus status is very tight, and the complex nature of this correlation likely limits any clinical application for cyclin D1 assessment.

[553]

**TÍTULO / TITLE:** - Old and new prognostic factors in acute myeloid leukemia with deranged core-binding factor beta.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Hematol. 2013 Apr 26. doi: 10.1002/ajh.23461.

●●Enlace al texto completo (gratis o de pago) [1002/ajh.23461](#)

**AUTORES / AUTHORS:** - Cairoli R; Beghini A; Turrini M; Bertani G; Nadali G; Rodeghiero F; Castagnola C; Lazzaroni F; Nichelatti M; Ferrara F; Pizzolo G; Pogliani E; Rossi G; Martinelli G; Morra E

**INSTITUCIÓN / INSTITUTION:** - Division of Haematology, Niguarda Hospital, Milan, Italy; Division of Haematology, Department of Internal Medicine, Valduce Hospital, Como, Italy.

**RESUMEN / SUMMARY:** - Acute myeloid leukemia (AML) with deranged core-binding factor beta (CBFbeta) is usually associated with a favorable prognosis with 50-70% of patients cured using contemporary treatments. We analyzed the prognostic significance of clinical features on 58 patients with CBFbeta-AML aged  $\leq 60$  years. Increasing age was the only predictor for survival ( $P < 0.001$ ), with an optimal cut-point at 43 years. White blood cells (WBCs) at diagnosis emerged as an independent risk factor for relapse incidence ( $P = 0.017$ ), with 1.1% increase of hazard for each  $1.0 \times 10^9 /L$  WBC increment. KIT mutations lacked prognostic value for survival and showed only a trend for relapse incidence ( $P = 0.069$ ). Am. J. Hematol., 2013. © 2013 Wiley Periodicals, Inc.

[554]

**TÍTULO / TITLE:** - GENETIC SUSCEPTIBILITY VARIANTS ASSOCIATED WITH COLORECTAL CANCER PROGNOSIS.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 May 27.

●●Enlace al texto completo (gratis o de pago) [1093/carcin/bgt179](#)

**AUTORES / AUTHORS:** - Abuli A; Lozano JJ; Rodriguez-Soler M; Jover R; Bessa X; Munoz J; Esteban-Jurado C; Fernandez-Rozadilla C; Carracedo A; Ruiz-Ponte C; Cubiella J; Balaguer F; Bujanda L; Rene JM; Clofent J; Morillas JD; Nicolas-Perez D; Xicola RM; Llor X; Pique JM; Andreu M; Castells A; Castellvi-Bel S

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Hospital Clinic, Centro de Investigación Biomedica en Red de Enfermedades Hepaticas y Digestivas (CIBEREHD), Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Catalonia, España.

**RESUMEN / SUMMARY:** - Colorectal cancer (CRC) is the second leading cause of cancer related death among men and women in Western countries. Once a tumour develops a differentiated prognosis could be determined by lifestyle habits or inherited and somatic genetic factors. Finding such prognostic factors will be helpful in order to identify cases with a shorter survival or at a higher risk of recurrence that may benefit from more intensive treatment and follow-up surveillance. Sixteen CRC genetic susceptibility variants were directly genotyped in a cohort of 1,235 CRC patients recruited by the EPICOLON Spanish consortium. Univariate Cox and multivariate regression analyses were performed taking as primary outcomes overall survival (OS), disease free survival (DFS) and recurrence-free interval (RFI). Genetic variants rs9929218 at 16q22.1 and rs10795668 at 10p14 may have an effect on OS. The G allele of rs9929218 was linked with a better OS (GG genotype, genotypic model: HR=0.65 95%CI 0.45-0.93 P=0.0179; GG/GA genotypes, dominant model: HR=0.66 95%CI 0.47-0.94 P=0.0202). Likewise, the G allele of rs10795668 was associated with better clinical outcome (GG genotype, genotypic model: HR=0.73 95%CI 0.53-1.01 P=0.0570; GA genotype, genotypic model: HR=0.66 95%CI 0.47-0.92 P=0.0137; GG/GA genotypes, dominant model: HR=0.68 95%CI 0.50-0.94 P=0.0194). In conclusion, CRC susceptibility variants rs9929218 and rs10795668 may exert some influence in modulating patient's survival and they deserve to be further tested in additional CRC cohorts in order to confirm their potential as prognosis or predictive biomarkers.

[555]

**TÍTULO / TITLE:** - Preclinical data and early clinical experience supporting the use of histone deacetylase inhibitors in multiple myeloma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 Jul;37(7):829-37. doi: 10.1016/j.leukres.2013.03.006. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.03.006](#)

**AUTORES / AUTHORS:** - Richardson PG; Mitsiades CS; Laubach JP; Hajek R; Spicka I; Dimopoulos MA; Moreau P; Siegel DS; Jagannath S; Anderson KC

**INSTITUCIÓN / INSTITUTION:** - Dana-Farber Cancer Institute, Boston, MA, USA. Electronic address: [paul\\_richardson@dfci.harvard.edu](mailto:paul_richardson@dfci.harvard.edu).

**RESUMEN / SUMMARY:** - Histone deacetylases (HDACs) mediate protein acetylation states, which in turn regulate normal cellular processes often dysregulated in cancer. These observations led to the development of HDAC inhibitors that target tumors through multiple effects on protein acetylation. Clinical evidence demonstrates that treatment with HDAC inhibitors (such as vorinostat, panobinostat, and romidepsin) in combination with other antimyeloma agents (such as proteasome inhibitors and immunomodulatory drugs) has promising antitumor activity in relapsed/refractory multiple myeloma patients. This mini-review highlights the role of protein acetylation in the development of cancers and the rationale for the use of HDAC inhibitors in this patient population.

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[556]

**TÍTULO / TITLE:** - Increased alpha-Tubulin1b Expression Indicates Poor Prognosis and Resistance to Chemotherapy in Hepatocellular Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dig Dis Sci. 2013 Apr 27.

●●Enlace al texto completo (gratis o de pago) [1007/s10620-013-2692-](#)

[Z](#)

**AUTORES / AUTHORS:** - Lu C; Zhang J; He S; Wan C; Shan A; Wang Y; Yu L; Liu G; Chen K; Shi J; Zhang Y; Ni R

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Affiliated Hospital of Nantong University, 20 Xisi Road, Nantong, 226001, Jiangsu Province, People's Republic of China.

**RESUMEN / SUMMARY:** - BACKGROUND: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide. It is important to understand molecular mechanisms of HCC progression and to develop clinically useful biomarkers for the disease. AIM: We aimed to investigate the possible involvement of alpha-tubulin1b (TUBA1B) in HCC pathology. METHODS: Tissue specimens were obtained from 114 HCC patients during hepatectomy. Immunohistochemistry and western blot analysis were used to detect TUBA1B expression in HCC tissues and cell lines. TUBA1B was knocked down in HCC cells by siRNA transfection. CCK-8 assay and flow cytometry were applied to determine cell proliferation and cell cycle progression, respectively. The efficacy

of paclitaxel chemotherapy was evaluated by plate colony formation assay. RESULTS: TUBA1B was higher expressed in HCC tumor tissues than in adjacent nontumor tissues. TUBA1B and Ki-67 expressions were positively related to each other, and both their expressions were significantly associated with histological grade of HCC patients. Univariate and multivariate survival analyses revealed that TUBA1B was a significant predictor for overall survival of HCC patients. TUBA1B expression was increased in HCC cells during the G1- to S-phase transition. TUBA1B knockout in HCC cells inhibited cell proliferation, and attenuated resistance to paclitaxel. CONCLUSIONS: Our results indicated that TUBA1B expression was upregulated in HCC tumor tissues and proliferating HCC cells, and an increased TUBA1B expression was associated with poor overall survival and resistance to paclitaxel of HCC patients.

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[557]

**TÍTULO / TITLE:** - Limoniastrum guyonianum aqueous gall extract induces apoptosis in human cervical cancer cells involving p16INK4A re-expression related to UHRF1 and DNMT1 down-regulation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Exp Clin Cancer Res. 2013 May 20;32(1):30.

●●Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-30](#)

**AUTORES / AUTHORS:** - Krifa M; Alhosin M; Muller CD; Gies JP; Chekir-Ghedira L; Ghedira K; Mely Y; Bronner C; Mousli M

**RESUMEN / SUMMARY:** - Several reports have described the potential effects of natural compounds as anti-cancer agents in vitro as well as in vivo. The aim of this study was to evaluate the anti-cancer effect of Limoniastrum guyonianum aqueous gall extract (G extract) and luteolin in the human cervical cancer HeLa cell line, and, if so, to clarify the underlying mechanism. Our results show that G extract and luteolin inhibited cell proliferation and induced G2/M cell cycle arrest in a concentration and time-dependent manner. Both natural products induced programmed cell death as confirmed by the presence of hypodiploid G0/G1 cells. These effects are associated with an up-regulation of the expression of the tumor suppressor gene p16INK4A and a down-regulation of the expression of the anti-apoptotic actor UHRF1 and its main partner DNMT1. Moreover, G extract- and luteolin-induced UHRF1 and DNMT1 down-regulation is accompanied with a global DNA hypomethylation in HeLa cell line. Altogether our results show that G extract mediates its growth inhibitory effects on human cervical cancer HeLa cell line likely via the activation of a p16INK4A -dependent cell cycle checkpoint signalling pathway orchestrated by UHRF1 and DNMT1 down-regulation.

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[558]

**TÍTULO / TITLE:** - 2-Hydroxy-3-methylantraquinone from *Hedyotis diffusa* Willd induces apoptosis in human leukemic U937 cells through modulation of MAPK pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Pharm Res. 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago) [1007/s12272-013-0096-4](http://1007/s12272-013-0096-4)

**AUTORES / AUTHORS:** - Wang N; Li DY; Niu HY; Zhang Y; He P; Wang JH

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatrics, Shengjing Hospital of China Medical University, Shenyang, 110004, China.

**RESUMEN / SUMMARY:** - The herb of *Hedyotis diffusa* Willd (*H. diffusa* Willd), an annual herb distributed in northeastern Asia, has been known as a traditional oriental medicine for the treatment of cancer. Recently, Chinese researchers have discovered that two anthraquinones isolated from a water extract of *H. diffusa* Willd showed apoptosis-inducing effects against cancer cells. However, the cellular and molecular mechanisms responsible for this phenomenon are poorly understood. The current study determines the role of mitogen-activated protein kinases (MAPK) in human leukemic U937 cells apoptosis induced by 2-hydroxy-3-methylantraquinone from *H. diffusa*. Our results showed that 2-hydroxy-3-methylantraquinone decreased phosphorylation-ERK1/2 (p-ERK1/2), and increased p-p38MAPK, but did not affect expressions of p-JNK1/2 in U937 cells. Moreover, treatment of U937 cells with 2-hydroxy-3-methylantraquinone resulted in activation of caspase-3. Furthermore, PD98059 (ERK1/2 inhibitor) significantly enhanced 2-hydroxy-3-methylantraquinone-induced apoptosis in U937 cells, whereas caspase-3 inhibitor or SB203580 (p-p38MAPK inhibitor), decreased apoptosis in U937 cells. Taken together, our study for the first time suggests that 2-hydroxy-3-methylantraquinone is able to enhance apoptosis of U937 cells, at least in part, through activation of p-p38MAPK and downregulation of p-ERK1/2. Moreover, the triggering of caspase-3 activation mediated apoptotic induction.

[559]

**TÍTULO / TITLE:** - 2-(2-Methylfuran-3-carboxamido)-3-phenylpropanoic acid, a potential CYP26A1 inhibitor to enhance all-trans retinoic acid-induced leukemia cell differentiation based on virtual screening and biological evaluation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem. 2013 Jun 1;21(11):3256-61. doi: 10.1016/j.bmc.2013.03.044. Epub 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmc.2013.03.044](http://1016/j.bmc.2013.03.044)

**AUTORES / AUTHORS:** - Li F; Zhao D; Ren J; Hao F; Liu G; Jin S; Jing Y; Cheng M

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Structure-Based Drugs Design & Discovery of Ministry of Education, School of Pharmaceutical Engineering,

Shenyang Pharmaceutical University, 103 Wenhua Road, Shenhe District, Shenyang 110016, PR China.

**RESUMEN / SUMMARY:** - To develop new CYP26A1 inhibitors, a three-cycle virtual screening was carried out based on the constructed homology model of human CYP26A1 using Dock, Fred, Gold and AutoDock. Twenty-two compounds exhibited high scores and reasonable binding modes in molecular docking were purchased from Specs Company. Eighteen compounds were tested their abilities to enhance ATRA-induced differentiation in human acute promyelocytic leukemia NB4 cells. Eight of them enhanced the ability of ATRA to induce differentiation at concentrations of 0.5 and 1 μM. Among these compounds, 2-(2-methylfuran-3-carboxamido)-3-phenylpropanoic acid (S8) is of most effective in blocking ATRA breaking down in NB4 cells based on the LC-MS/MS assay.

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[560]

**TÍTULO / TITLE:** - Effects of an Inhibitor of the Gamma-Secretase Complex on Proliferation and Apoptotic Parameters in a FOXL2-Mutated Granulosa Tumor Cell Line (KGN).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biol Reprod. 2013 May 22.

●●Enlace al texto completo (gratis o de pago)

[1095/biolreprod.113.108100](http://1095/biolreprod.113.108100)

**AUTORES / AUTHORS:** - Irusta G; Pazos MC; Abramovich D; De Zuniga I; Parborell F; Tesone M

**RESUMEN / SUMMARY:** - Ovarian granulosa cell tumors (GCTs) represent 3-5% of all ovarian malignancies. Treatments have limited proven efficacy and biologically targeted treatment is lacking. The aim of this study was to investigate the role of Notch signaling in the proliferation, steroidogenesis, apoptosis, and PI3K/AKT pathway in a FOXL2-mutated granulosa tumor cell line (KGN), representative of the adult form of GCTs. When Notch signaling is initiated, the receptors expose a cleavage site in the extracellular domain to the metalloproteinase TACE and, following this cleavage, Notch undergoes another cleavage mediated by the presenilin-gamma-secretase complex. To achieve our goal, DAPT, an inhibitor of the gamma-secretase complex, was used to investigate the role of the Notch system in parameters associated with cell growth and death, using a human granulosa cell tumor line (KGN) as an experimental model. We observed that JAGGED1, DLL4, NOTCH1 and NOTCH4 were highly expressed in KGN cells as compared to granulosa-lutein cells obtained from ART patients. The proliferation and viability of KGN cells, as well as progesterone and estradiol production, decreased in the presence of 20 μM DAPT. Apoptotic parameters like PARP and caspase 8 cleavages, BAX and BCLXshort increased in KGN cells cultured with DAPT, while others such as BCL2, BCLXlong, FAS and FASL did not change. AKT phosphorylation

decreased and PTEN protein increased when Notch signaling was inhibited in KGN cells. We conclude that the Notch system acts as a survival pathway in KGN cells, and might be interacting with the PI3K/AKT pathway.

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[561]

**TÍTULO / TITLE:** - Toxicity and prognosis in overweight and obese women with lung cancer receiving Carboplatin-Paclitaxel doublet chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Invest. 2013 May;31(4):251-7. doi: 10.3109/07357907.2013.784778. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago)

[3109/07357907.2013.784778](#)

**AUTORES / AUTHORS:** - Kashiwabara K; Yamane H; Tanaka H

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan.

**RESUMEN / SUMMARY:** - We retrospectively analyzed overdosing-related toxicity and prognosis in 127 women with lung cancer receiving carboplatin (6AUC) estimated by the Cockcroft-Gault formula using actual body weight and paclitaxel (200 mg/m<sup>2</sup>). Between the body mass index (BMI) > 25 group (n = 42) and the BMI ≤ 25 group (n = 85), there was no difference in dose intensity of carboplatin (122 mg/m<sup>2</sup>/week vs. 124 mg/m<sup>2</sup>/week, p = .323), median overall survival (285 days vs. 282 days, p = .820), and toxicity, except Grade 4 neutropenia in the second cycle. Women with BMI > 25 did not have an increased risk of toxicity because of an appropriate dose reduction.

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[562]

**TÍTULO / TITLE:** - Cinnamic acid induces apoptotic cell death and cytoskeleton disruption in human melanoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Exp Clin Cancer Res. 2013 May 23;32:31. doi: 10.1186/1756-9966-32-31.

●●Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-31](#)

**AUTORES / AUTHORS:** - Niero EL; Machado-Santelli GM

**INSTITUCIÓN / INSTITUTION:** - Department of Cell and Developmental Biology, Institute of Biomedical Sciences, University of Sao Paulo, Av, Prof, Lineu Prestes, 1524, Cidade Universitaria, 05508-000 Sao Paulo, SP, Brazil.

[glauca.santelli@gmail.com](mailto:glauca.santelli@gmail.com).

**RESUMEN / SUMMARY:** - Anticancer activities of cinnamic acid derivatives include induction of apoptosis by irreversible DNA damage leading to cell death. The present work aimed to compare the cytotoxic and genotoxic potential of cinnamic acid in human melanoma cell line (HT-144) and human melanocyte cell line derived from blue nevus (NGM). Viability assay showed that the IC<sub>50</sub>

for HT-144 cells was 2.4 mM, while NGM cells were more resistant to the treatment. The growth inhibition was probably associated with DNA damage leading to DNA synthesis inhibition, as shown by BrdU incorporation assay, induction of nuclear aberrations and then apoptosis. The frequency of cell death caused by cinnamic acid was higher in HT-144 cells. Activated-caspase 3 staining showed apoptosis after 24 hours of treatment with cinnamic acid 3.2 mM in HT-144 cells, but not in NGM. We observed microtubules disorganization after cinnamic acid exposure, but this event and cell death seem to be independent according to M30 and tubulin labeling. The frequency of micronucleated HT-144 cells was higher after treatment with cinnamic acid (0.4 and 3.2 mM) when compared to the controls. Cinnamic acid 3.2 mM also increased the frequency of micronucleated NGM cells indicating genotoxic activity of the compound, but the effects were milder. Binucleation and multinucleation counting showed similar results. We conclude that cinnamic acid has effective antiproliferative activity against melanoma cells. However, the increased frequency of micronucleation in NGM cells warrants the possibility of genotoxicity and needs further investigation.

[563]

**TÍTULO / TITLE:** - YL529, a novel, orally available multikinase inhibitor, potently inhibits angiogenesis and tumor growth in preclinical models.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Pharmacol. 2013 Apr 17. doi: 10.1111/bph.12216.

●●Enlace al texto completo (gratis o de pago) [1111/bph.12216](#)

**AUTORES / AUTHORS:** - Xu YZ; Lin HJ; Meng NN; Lu WJ; Li G; Han YY; Dai XY; Xia Y; Song XR; Yang SY; Wei YQ; Yu LT; Zhao YL

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China.

**RESUMEN / SUMMARY:** - BACKGROUND AND PURPOSE: Targeted chemotherapy using small-molecule inhibitors of angiogenesis and proliferation is a promising strategy for cancer therapy. EXPERIMENTAL APPROACH: N-methyl-4-(4-(3-(trifluoromethyl)benzamido)phenoxy)picolinamide-4-methylbenzenesulfonate (YL529) was developed via computer-aided drug design, de novo synthesis and high-throughput screening. The biochemical, pharmacodynamical, and toxicological profiles of YL529 were investigated using kinase and cell viability assay, zebrafish and mice tumor xenograft models. KEY RESULTS: In vitro, YL529 selectively inhibited the activities of vascular endothelial growth factor receptors VEGFR2/VEGFR3 and serine/threonine kinase RAF kinase. YL529 inhibited VEGF165-induced phosphorylation of VEGFR2, as well as proliferation, migration, invasion and tube formation of human umbilical vascular endothelial cells (HUVECs). It also significantly blocked vascular formation and angiogenesis in zebrafish model. Moreover,

YL529 strongly attenuated the proliferation of A549 cell line through disrupting RAF/MEK/MAPK (mitogen-activated protein kinase) pathway. Oral administration of YL529 (37.5-150 mg-1 .kg-1 .day-1 ) to nude mice bearing established tumor xenografts significantly prevented the growth (60-80%) of A549, SPC-A1, A375, OS-RC-2 and HCT116 tumors without detectable toxicity. Tumors from animals inoculated with the lung cancer cell lines SPC-A1 and A549 and the colon carcinoma cell line HCT116 revealed that YL529 treatment markedly reduced microvessel density and increased tumor cell apoptosis. CONCLUSIONS AND IMPLICATIONS: YL529, an orally active multikinase inhibitor, shows the therapeutic potential for solid tumors, and warrants further investigation as a candidate anticancer agent.

[564]

**TÍTULO / TITLE:** - The role of systemic inflammatory and nutritional blood-borne markers in predicting response to neoadjuvant chemotherapy and survival in oesophagogastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):596. doi: 10.1007/s12032-013-0596-6. Epub 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0596-](#)

[6](#)

**AUTORES / AUTHORS:** - Noble F; Hopkins J; Curtis N; Kelly JJ; Bailey IS; Byrne JP; Bateman AC; Bateman AR; Underwood TJ

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, Hampshire, SO16 6YD, UK.

**RESUMEN / SUMMARY:** - The aim of this study was to interrogate whether blood-borne inflammatory and nutritional markers predict long-term survival and response to neoadjuvant chemotherapy in radically treated oesophagogastric cancer patients. This retrospective study included 246 patients who underwent oesophageal resection for high-grade dysplasia or carcinoma between 2005 and 2010. The predictive value of routine preoperative immunonutritional blood tests was assessed for their association with survival and response to chemotherapy. On multivariate analysis, higher neutrophil-lymphocyte ratio (NLR) ( $p < 0.0001$ ), N stage ( $p < 0.0001$ ) and perineural invasion ( $p < 0.0001$ ) were associated with poor overall survival. Regarding disease-free survival, multivariate analysis showed reduced serum albumin ( $p = 0.034$ ), N stage ( $p < 0.0001$ ), M stage ( $p = 0.037$ ), vascular invasion ( $p < 0.0001$ ) and presence of R1 resection ( $p = 0.003$ ) to correlate with earlier recurrence. In those who received neoadjuvant chemotherapy, analysis of prechemotherapy characteristics showed only serum albumin ( $p = 0.037$ ) to predict pathological response to chemotherapy. Preoperative immunonutritional markers, NLR and albumin, were independent prognostic markers for overall survival and disease-

free survival, respectively, after oesophageal cancer resection. Prospective studies evaluating the role of immunonutritional modulation to improve response to chemotherapy and long-term outcome are required.

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[565]

**TÍTULO / TITLE:** - MicroRNA-205, a novel regulator of the anti-apoptotic protein Bcl2, is downregulated in prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):307-14. doi: 10.3892/ijo.2013.1915. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1915](#)

**AUTORES / AUTHORS:** - Verdoodt B; Neid M; Vogt M; Kuhn V; Liffers ST; Palisaar RJ; Noldus J; Tannapfel A; Mirmohammadsadegh A

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, Ruhr-University Bochum, D-44789 Bochum, Germany.

**RESUMEN / SUMMARY:** - Decreased expression of the microRNA miR-205 has been observed in multiple tumour types due to its role in the epithelial to mesenchymal transition, which promotes metastasis. We determined the expression of miR-205 in 111 archival samples of prostate carcinoma and found it to be strongly reduced in most samples, with a median expression level of 16% in comparison to benign tissue from the same patient. Lower miR-205 expression correlated significantly with tumour size and miR-205 levels decreased with increasing Gleason score from 7a=3+4 to 8=4+4. In addition, we describe the anti-apoptotic protein BCL2 as a target of miR-205, relevant for prostate cancer due to its role in prognosis of primary tumours and in the appearance of androgen independence. The repression of BCL2 by miR-205 was confirmed using reporter assays and western blotting. BCL2 mRNA expression in the same collective of prostate cancer tissue samples was associated with higher Gleason score and extracapsular extension of the tumour (pT3). Consistent with its anti-apoptotic target BCL2, miR-205 promoted apoptosis in prostate cancer cells in response to DNA damage by cisplatin and doxorubicin in the prostate cancer cell lines PC3 and LnCap. MiR-205 also inhibited proliferation in these cell lines.

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[566]

**TÍTULO / TITLE:** - Apoptosis induction and G2/M arrest of 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone from *Rubia yunnanensis* in human cervical cancer HeLa cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmazie. 2013 Apr;68(4):293-9.

**AUTORES / AUTHORS:** - Zeng GZ; Fan JT; Xu JJ; Li Y; Tan NH

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, P. R. China.

**RESUMEN / SUMMARY:** - 2-Methyl-1,3,6-trihydroxy-9,10-anthraquinone (MTA), one of the major components isolated from the traditional Chinese medicine *Rubia yunnanensis*, exhibited inhibitory activity on the proliferation of several human cancer cell lines. The results from an annexin V-FITC (fluorescein-5-isothiocyanate) apoptosis assay and DNA content analysis showed that MTA exerted cytotoxicity via apoptosis induction and G2/M cell cycle arrest in human cervical carcinoma HeLa cells. Further, MTA was found to induce apoptosis of HeLa cells through the mitochondria-mediated pathway. It caused the translocation of Bax to the mitochondria and release of cytochrome c into the cytosol, which caused the cleavage of caspase and poly(ADP-ribose) polymerase and finally triggered the apoptosis. Furthermore, the p53/p21/Cdc2-cyclin B1 signaling was found related to the G2/M arrest caused by MTA. The over-expression of p21 and down-expression of cyclin B1 caused by MTA inactivated the Cdc2-cyclin B1 complex of G2/M checkpoint and finally caused the G2/M arrest in HeLa cells. This study demonstrated that MTA is a potential anti-cancer component of *R. yunnanensis*, a folk anti-cancer herb used in Yunnan, China.

[567]

**TÍTULO / TITLE:** - Goserelin can inhibit ovarian cancer proliferation and simultaneously protect ovarian function from cisplatin: an in vitro and in vivo study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Chemother. 2013;25(2):96-103. doi: 10.1179/1973947813Y.0000000069.

●●Enlace al texto completo (gratis o de pago)

[1179/1973947813Y.0000000069](#)

**AUTORES / AUTHORS:** - Zhang Y; Ding JX; Tao X; Lu ZY; Wang JJ; Feng WW; Hua KQ

**INSTITUCIÓN / INSTITUTION:** - The Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China.

**RESUMEN / SUMMARY:** - This study investigates whether goserelin can inhibit ovarian cancer proliferation and protect ovarian function from cisplatin (CDDP). We evaluated proliferation and AKT phosphorylation in goserelin-treated ES-2 and SKOV3-ip ovarian cancer cells. Anti-Mullerian hormone (AMH) in human granulosa cells (hGCs) cotreated with goserelin and CDDP was measured by ELISA. Tumour volumes, Ki-67 expression, estrus, follicles, ovarian volumes, and serum AMH were compared in nude mice bearing transplanted tumours treated with goserelin and/or CDDP. Our results showed that goserelin inhibited cellular proliferation and AKT phosphorylation in vitro, and inhibited tumour

growth and Ki-67 expression in vivo. Goserelin and CDDP cotreatment decreased the estrus cycles of the nude mice and prolonged estrus duration. Goserelin abrogated the CDDP-induced down-regulation of primary and preantral follicle percentage and ovarian volume. Goserelin increased AMH secretion in vitro and in vivo. In conclusion, goserelin inhibited ovarian cancer proliferation and simultaneously protected ovarian function from CDDP.

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[568]

**TÍTULO / TITLE:** - MicroRNA-98 sensitizes cisplatin-resistant human lung adenocarcinoma cells by up-regulation of HMGA2.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmazie. 2013 Apr;68(4):274-81.

**AUTORES / AUTHORS:** - Xiang Q; Tang H; Yu J; Yin J; Yang X; Lei X

**INSTITUCIÓN / INSTITUTION:** - Institute of Pharmacy and Pharmacology, P.R. China.

**RESUMEN / SUMMARY:** - This study was done to explore the role of microRNA-98 (miR-98) in cisplatin sensitization in human lung adenocarcinoma cell line. Differential expressions of miRNAs were analysed between cisplatin-resistant human lung adenocarcinoma cell line A549/DDP and its parental cell A549 by miRNAs microarray, of which 14 miRNAs were showed to be significantly (>2-fold) up-regulated and 8 miRNAs had marked down-regulation (<0.5-fold) in A549/DDP cells compared with in A549 cells. MiR-98, a member in the let-7 family, acts as a negative regulator in the expression of HMGA2 (high mobility group A2) oncogene, and it has been shown to have a nearly 3-fold decrease in A549/DDP cells. We found that elevated expression of miR-98 led to a higher sensitivity of A549/DDP cells to cisplatin, and the protein level of HMGA2, was clearly up-regulated in both A549/DDP and A549 cells by miR-98. Moreover, both Bcl-XL and Bcl-2, were down-regulated in the Pre-miR-98™ transfectants cells. We for the first time demonstrated that the expression of miR-98 increases cells spontaneous apoptosis and sensitizes cells to cisplatin at least in part via HMGA2 up-regulation. Our findings provided insight into some specific miRNAs in lung cancer as potential therapeutic targets.

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[569]

**TÍTULO / TITLE:** - Oncostatin M is a FIP1L1/PDGFRα-dependent mediator of cytokine production in chronic eosinophilic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Allergy. 2013 Jun;68(6):713-23. doi: 10.1111/all.12139. Epub 2013 Apr 27.

●●Enlace al texto completo (gratuito o de pago) [1111/all.12139](http://1111/all.12139)

**AUTORES / AUTHORS:** - Hoermann G; Cerny-Reiterer S; Sadovnik I; Mullauer L; Bilban M; Groger M; Horny HP; Reiter A; Schmitt-Graeff A; Mannhalter C; Valent P; Mayerhofer M

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Chronic eosinophilic leukemia (CEL) is a myeloproliferative neoplasm characterized by expansion of neoplastic eosinophils, tissue infiltration, and organ damage. In a subset of these patients, the FIP1L1/PDGFR $\alpha$  (F/P) oncoprotein is detectable. F/P exhibits constitutive tyrosine kinase activity and activates a number of signaling pathways. So far, however, little is known about the role of F/P-dependent proteins in the pathogenesis of CEL. **METHODS:** A screen for F/P-dependent cytokines was performed in growth factor-dependent human cell lines lentivirally transduced with F/P. Signal transduction pathways were characterized in Ba/F3 cells with doxycycline-inducible expression of F/P and in EOL-1 cells. Cytokine expression was confirmed in patients' material by immunohistochemistry, immunofluorescence, and confocal microscopy. Gene expression analysis, proliferation assays, and chemotaxis assays were used to elucidate paracrine interactions between neoplastic eosinophils and stromal cells. **RESULTS:** We show that F/P upregulates expression of oncostatin M (OSM) in various cell line models in a STAT5-dependent manner. Correspondingly, neoplastic eosinophils in the bone marrow were found to overexpress OSM. OSM derived from F/P + cells stimulated proliferation of stromal cells. Moreover, OSM-containing supernatants from F/P + cells were found to upregulate production of stromal cell-derived factor-1 (SDF-1)/CXCL12 in human fibroblasts. SDF-1, in turn, induced migration of EOL-1 cells in a dose-dependent manner. **CONCLUSIONS:** We have identified a F/P-driven paracrine interaction between neoplastic eosinophils and stromal cells that may contribute to tissue fibrosis and accumulation of neoplastic eosinophils in CEL.

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[570]

**TÍTULO / TITLE:** - Cell diameter measurements obtained with a handheld cell counter could be used as a surrogate marker of G2/M arrest and apoptosis in colon cancer cell lines exposed to SN-38.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 17;434(4):753-9. doi: 10.1016/j.bbrc.2013.03.128. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.03.128](https://doi.org/10.1016/j.bbrc.2013.03.128)

**AUTORES / AUTHORS:** - Tahara M; Inoue T; Miyakura Y; Horie H; Yasuda Y; Fujii H; Kotake K; Sugano K

**INSTITUCIÓN / INSTITUTION:** - Oncogene Research Unit/Cancer Prevention Unit, Tochigi Cancer Center Research Institute, Utsunomiya, Tochigi, Japan;

Department of Gastrointestinal Surgery, Jichi Medical University, Shimotsuke, Tochigi, Japan.

**RESUMEN / SUMMARY:** - In vitro assessment of chemosensitivity are important for experiments evaluating cancer therapies. The Scepter 2.0 cell counter, an automated handheld device based on the Coulter principle of impedance-based particle detection, enables the accurate discrimination of cell populations according to cell size and volume. In this study, the effects of SN-38, the active metabolite of irinotecan, on the colon cancer cell lines HCT116 and HT29 were evaluated using this device. The cell count data obtained with the Scepter counter were compared with those obtained with the (3)H-thymidine uptake assay, which has been used to measure cell proliferation in many previous studies. In addition, we examined whether the changes in the size distributions of these cells reflected alterations in the frequency of cell cycle arrest and/or apoptosis induced by SN-38 treatment. In our experiments using the Scepter 2.0 cell counter, the cell counts were demonstrated to be accurate and reproducible measure and alterations of cell diameter reflected G2/M cell cycle arrest and apoptosis. Our data show that easy-to-use cell counting tools can be utilized to evaluate the cell-killing effects of novel treatments on cancer cells in vitro.

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[571]

**TÍTULO / TITLE:** - Overexpression of RING box protein-1 (RBX1) associated with poor prognosis of non-muscle-invasive bladder transitional cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Surg Oncol. 2013 Jun;107(7):758-61. doi: 10.1002/jso.23317. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1002/jso.23317](http://1002/jso.23317)

**AUTORES / AUTHORS:** - Wang W; Qiu J; Liu Z; Zeng Y; Fan J; Liu Y; Guo Y

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Shanghai First People's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; Department of Urology, The Fourth Affiliated Hospital of Nantong University (Yancheng First People's Hospital), Jiangsu, China.

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVE: RING box protein-1 (RBX1) is a key subunit of the ubiquitin E3 ligase Skp1/Cullin1/Rbx1/F-box protein complex. Altered expression RBX1 is shown to associate with tumorigenesis and tumor progression. This study detected RBX1 expression for association with clinical significance (such as clinicopathological data and survival of the patients) in non-muscle-invasive bladder transitional cell carcinoma (NMIBC). METHODS: A total of 70 primary NMIBC tissue specimens and 24 normal tissue specimens were recruited and analyzed immunohistochemically for expression of RBX1 protein and associated with clinicopathological data and survival of the patients. RESULTS: RBX1 was highly expressed in NMIBC, but was lowly expressed in the normal tissue.

RBX1 expression was associated with high tumor grade and advanced clinical stage ( $P < 0.01$  and  $P < 0.05$ , respectively). Moreover, patients with high RBX1 expression had shorter recurrence-free survival and progression-free survival rates ( $P < 0.001$  and  $P < 0.01$ , respectively). Multivariate analysis demonstrated that RBX1 expression is an independent prognostic factor for tumor recurrence and progression of NMIBC ( $P < 0.05$ ). CONCLUSIONS: Overexpression of RBX1 protein contributes to tumor progression and poor prognosis of NMIBC. J. Surg. Oncol. 2013;107:758-761. © 2013 Wiley Periodicals, Inc.

[572]

**TÍTULO / TITLE:** - D-dimer elevation and paresis predict thromboembolic events during bevacizumab therapy for recurrent malignant glioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):2093-8.

**AUTORES / AUTHORS:** - Misch M; Czabanka M; Dengler J; Stoffels M; Auf G; Vajkoczy P; Stockhammer F

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, University Medicine Gottingen, Robert-Koch-Str. 40, 37075 Gottingen, Germany.

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**RESUMEN / SUMMARY:** - BACKGROUND: The major side-effects of bevacizumab in glioma treatment are venous thromboembolic events (VTE). We retrospectively evaluated factors potentially predictive of thromboembolic events. PATIENTS AND METHODS: Bevacizumab, alone or in combination with chemotherapy was used as salvage therapy for recurrence in malignant glioma every two weeks. None but one patient received anti-coagulants. Before each bevacizumab cycle differential blood cell count, kidney and liver parameters, D-dimers, neurological status, body-mass index, vital signs and signs of venous thrombosis were assessed. RESULTS: Thirty-eight patients received 428 cycles of bevacizumab. In five patients (13%), six VTE were observed. These complications were preceded four weeks before the onset of symptoms by D-dimer elevation above 0.865 mg/l [ $p < 0.0001$ ; sensitivity=89% (95% confidence interval=83-93%); specificity=89% (95% CI=52-100%)]. An existing hemiparesis constituted a 27-fold risk elevation for thrombotic complication ( $p < 0.0001$ , chi(2)-test). CONCLUSION: D-Dimer elevation or hemiparesis predict VTE under bevacizumab and chemotherapy, four weeks before the event becomes clinically apparent. Future investigations should determine if prophylactic anti-coagulants for patients at risk may reduce the risk of VTE.

[573]

**TÍTULO / TITLE:** - Immunohistochemical expression of core 2 beta1,6-N-acetylglucosaminyl transferase 1 (C2GnT1) in endometrioid-type endometrial carcinoma: a novel potential prognostic factor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Histopathology. 2013 Jun;62(7):986-93. doi: 10.1111/his.12107. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [1111/his.12107](#)

**AUTORES / AUTHORS:** - Miyamoto T; Suzuki A; Asaka R; Ishikawa K; Yamada Y; Kobara H; Nakayama J; Shiozawa T

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynaecology, Shinshu University School of Medicine, Matsumoto, Japan.

**RESUMEN / SUMMARY:** - AIMS: It has been reported that the expression of core 2 beta1,6-N-acetylglucosaminyl transferase 1 (C2GnT1), which synthesizes the core 2 branching structure on O-glycans, may be associated with the biological aggressiveness of tumour cells. Therefore, the aim of this study was to examine the relationship between the expression of C2GnT1 and clinicopathological parameters of patients with endometrial carcinoma. METHODS AND RESULTS: The immunohistochemical expression of C2GnT1 was examined in 84 cases of endometrioid-type endometrial carcinoma, 15 cases of endometrial hyperplasia, and 30 normal endometria. The staining intensity was reported according to a positivity index (PI, full score 100), calculated from the percentage of positive cells. The expression of C2GnT1 was significantly higher in endometrial carcinoma (PI = 8.31 +/- 15.29) than in normal endometrium (PI = 0.52 +/- 1.24) (P < 0.0005). In carcinomas, the PI was higher in high-grade or advanced-stage tumours, but not significantly. Topologically, C2GnT1 was strongly expressed at sites of deep myometrial invasion. In addition, patients with C2GnT1 overexpression (PI >= 10) had significantly shorter survival (P < 0.0005). Multivariable analysis also indicated that C2GnT1 overexpression was an independent prognostic factor (P = 0.017). CONCLUSIONS: C2GnT1 appears to be involved in the biological aggressiveness of endometrial carcinoma. C2GnT1 might become a novel prognostic factor for endometrial carcinoma.

[574]

**TÍTULO / TITLE:** - Furanodiene Presents Synergistic Anti-proliferative Activity With Paclitaxel Via Altering Cell Cycle and Integrin Signaling in 95-D Lung Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Phytother Res. 2013 Apr 3. doi: 10.1002/ptr.4984.

●●Enlace al texto completo (gratis o de pago) [1002/ptr.4984](#)

**AUTORES / AUTHORS:** - Xu WS; Dang YY; Chen XP; Lu JJ; Wang YT

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, China.

**RESUMEN / SUMMARY:** - Furanodiene (FUR) is a natural terpenoid isolated from *Rhizoma Curcumae*, a well-known Chinese medicinal herb that presents anti-proliferative activities in several cancer cell lines. Recently, we found that the combined treatment of FUR with paclitaxel (TAX) showed synergetic anti-proliferative activities in 95-D lung cancer cells. Herein, we showed that FUR reduced the cell numbers distributed in mitosis phase induced by TAX while increased those in G1 phase. The protein levels of cyclin D1, cyclin B1, CDK6 and c-Myc were all down-regulated in the group of combined treatment. The dramatically down-regulated expression of integrin beta4, focal adhesion kinase and paxillin might partially contribute to the synergic effect. Though FUR alone obviously induced endoplasmic reticulum stress, this signaling pathway may not contribute to the synergetic anti-proliferative effect as the protein expression of CHOP and BIP was similar in FUR alone and combined treatment group.  
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[575]

**TÍTULO / TITLE:** - Analysis of the EGFR mutation status in head and neck squamous cell carcinoma before treatment with Gefitinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Onkologie*. 2013;36(4):161-6. doi: 10.1159/000349941. Epub 2013 Mar 18.

●●Enlace al texto completo (gratis o de pago) [1159/000349941](#)

**AUTORES / AUTHORS:** - Bontognali S; Pless M; Brutsche MH; Fischer C; Rochlitz C; Buess M

**INSTITUCIÓN / INSTITUTION:** - Kopf-Hals-Tumor-Zentrum, Universitätsspital Basel, Switzerland.

**RESUMEN / SUMMARY:** - BACKGROUND: The efficacy of chemotherapy in metastatic and recurrent squamous cell carcinomas of the head and neck (HNSCC) remains unsatisfactory. Gefitinib offers a new therapeutic option with comparable results and better tolerability than chemotherapy. We conducted this study to see if mutations in the epidermal growth factor receptor (EGFR) might predict the therapeutic benefit in HNSCC patients. PATIENTS AND METHODS: In a pilot trial, 8 patients with metastatic or recurrent HNSCC were treated palliatively with gefitinib (500 mg/day orally). Forceps biopsies were taken to confirm tumor recurrence and to perform an EGFR mutation analysis. RESULTS: The EGFR status could be determined in 6 of the 8 patients. 5 patients had no EGFR gene mutation, and 1 patient showed a silent guanine-to-adenosine mutation in position 2607. Even without any relevant mutation in the EGFR, we observed partial remission in 3 of 6 patients treated with gefitinib. We also observed that an additional 4 patients had stable disease for at least 10

weeks. The median progression-free survival was 6.25 months, and the median overall survival was 7.39 months. CONCLUSION: In HNSCC, there are tumor responses to gefitinib without protein-altering mutations in the EGFR gene.

[576]

**TÍTULO / TITLE:** - Association of Th1 and Th2 cytokines with transient inflammatory reaction during lenalidomide plus dexamethasone therapy in multiple myeloma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Hematol. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1007/s12185-013-1321-0](http://1007/s12185-013-1321-0)

**AUTORES / AUTHORS:** - Harada T; Ozaki S; Oda A; Fujii S; Nakamura S; Miki H; Kagawa K; Takeuchi K; Matsumoto T; Abe M

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine and Bioregulatory Sciences, Graduate School of Medical Sciences, University of Tokushima, 3-8-15 Kuramoto, Tokushima, 770-8503, Japan, [tkhr@clin.med.tokushima-u.ac.jp](mailto:tkhr@clin.med.tokushima-u.ac.jp).

**RESUMEN / SUMMARY:** - Transient inflammatory reactions have been reported in a subpopulation of patients with multiple myeloma (MM) during lenalidomide (Len) plus dexamethasone (DEX) therapy. Here, we examined serum levels of Th1 (IL-2 and IFN-gamma) and Th2 cytokines (IL-6 and TNF-alpha) in nine refractory or relapsed MM patients treated with Len plus low-dose DEX. Six patients showed elevation of C-reactive protein (CRP) after the initiation of therapy. In these patients, IFN-gamma and IL-6 were also elevated in two and three patients, respectively. The remaining three patients showed no appreciable changes in CRP or these cytokines. Furthermore, Len enhanced the production of both Th1 and Th2 cytokines in normal peripheral blood mononuclear cells and in patient bone marrow mononuclear cells containing primary myeloma cells and lymphocytes. These results suggest that the modulation of the Th1 and Th2 cytokine production by Len may contribute to transient inflammatory reaction in MM patients.

[577]

**TÍTULO / TITLE:** - Human leukocyte antigen class II alleles (DQB1 and DRB1) as predictors for response to interferon therapy in HCV genotype 4.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mediators Inflamm. 2013;2013:392746. doi: 10.1155/2013/392746. Epub 2013 Mar 14.

●●Enlace al texto completo (gratis o de pago) [1155/2013/392746](http://1155/2013/392746)

**AUTORES / AUTHORS:** - Shaker O; Bassiony H; El Raziky M; El-Kamary SS; Esmat G; El-Ghor AM; Mohamed MM

**INSTITUCIÓN / INSTITUTION:** - Departments of Medical Biochemistry & Molecular Biology, Faculty of Medicine, Cairo University, Cairo, Egypt.

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**RESUMEN / SUMMARY:** - Human leukocyte antigens class II play an important role in immune response against HCV. We investigated whether HLA class II alleles influence susceptibility to HCV infection and response to interferon therapy. HLA-DRB1 and -DQB1 loci were genotyped using PCR-SSO Luminex technology. According to our regimen, 41 (66%) of patients achieved sustained virological response to combined treatment of IFN and ribavirin. Frequencies of DQB1\*0313 allele and DRB1\*04-DRB1\*11, DQB1\*0204-DQB1\*0313, DQB1\*0309-DQB1\*0313, and DQB1\*0313-DQB1\*0319 haplotypes were significantly more frequent in nonresponders than in responders. In contrast, DQB1\*02, DQB1\*06, DRB1\*13, and DRB1\*15 alleles were significantly more frequent in responders than in nonresponders. Similarly, DRB1\*1301, DRB1\*1361, and DRB1\*1369 alleles and DRB1\*1301-DRB1\*1328, DRB1\*1301-DRB1\*1361, DRB1\*1301-DRB1\*1369, DRB1\*1328-DRB1\*1361, and DRB1\*1328-DRB1\*1369 haplotypes were significantly found only in responders. Some alleles and linkages showed significantly different distributions between patient and healthy groups. These alleles may be used as predictors for response to treatment or to susceptibility to HCV infection in the Egyptian population.

[578]

**TÍTULO / TITLE:** - Hypermethylation and prognostic implication of Syk gene in human colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):586. doi: 10.1007/s12032-013-0586-8. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0586-](#)

[8](#)

**AUTORES / AUTHORS:** - Yang Z; Huo L; Chen H; Ni B; Xiang J; Kang L; Wang L; Peng J; Yuan Y; Wang J

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University (Guangdong Gastrointestinal and Anal Hospital), Sun Yat-Sen University, Guangzhou, People's Republic of China.

**RESUMEN / SUMMARY:** - The study was aimed to investigate the relationship between hypermethylation of Syk gene and clinicopathological characteristics and long-term outcomes in colorectal cancer. The effect of Syk on cell proliferation and invasion ability was also assessed. Methylation and expression status of Syk were explored in CRC tissues and cell lines by MSP, qRT-PCR and western blot assay. The effects of Syk overexpression on tumorigenesis were studied by in vitro assay. The correlation between Syk methylation and

clinical relevance in CRC patients was also analyzed. Syk methylation was found 48.6 % in CRC tissue samples and 57.1 % in cell lines, respectively. The loss of Syk expression could be restored by demethylation agent. Overexpression of Syk in CRC cell inhibited cell proliferation ( $p < 0.01$ ) and invasion ( $p < 0.01$ ). The methylation of Syk was significantly associated with histological grade ( $p = 0.002$ ), lymph node status ( $p < 0.001$ ) and TNM stage ( $p < 0.001$ ). Five-year overall survival in methylated Syk group was significantly lower than that in unmethylated Syk group (59 vs. 80 %,  $p < 0.001$ ). Multivariate analysis demonstrated that Syk methylation was an independent prognostic factor for overall survival. Syk is identified as a potential tumor suppressor in CRC progression. Syk methylation is correlated with poor overall survival, which acts as an independent prognostic indicator of CRC.

[579]

**TÍTULO / TITLE:** - P2Y12 receptor inhibition augments cytotoxic effects of cisplatin in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):567. doi: 10.1007/s12032-013-0567-y. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0567-](#)

[y](#)

**AUTORES / AUTHORS:** - Sarangi S; Pandey A; Papa AL; Sengupta P; Koppam J; Dadwal U; Basu S; Sengupta S

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Brigham and Women's Hospital, Cambridge, MA 02139, USA.

**RESUMEN / SUMMARY:** - Expression of P2Y12 receptors has been documented in some cancer cell lines like C6 glioma, renal carcinoma and colon carcinoma. However, its direct role in altering response to chemotherapeutics has not been studied. In this study, we characterize the expression of P2Y12 receptor in breast cancer cell lines and evaluate its role in enhancing the cytotoxic effects of cisplatin. We observed a significant upregulation in P2Y12 expression in 4T1 breast cancer cell line with cisplatin treatment. Co-administration of P2Y12 inhibitor with cisplatin resulted in significantly higher cytotoxic response in 4T1 cancer cell line. This was mediated by HIF1 $\alpha$ -dependent upregulation of cellular apoptotic pathways. These findings identify P2Y12 receptor as a potential target to enhance antitumor efficacy of chemotherapeutic agents like cisplatin.

[580]

**TÍTULO / TITLE:** - Differential toxicity biomarkers for irinotecan- and oxaliplatin-containing chemotherapy in colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Jun;71(6):1463-72. doi: 10.1007/s00280-013-2145-6. Epub 2013 Mar 31.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2145-6](http://1007/s00280-013-2145-6)

**AUTORES / AUTHORS:** - Cortejoso L; Garcia MI; Garcia-Alfonso P; Gonzalez-Haba E; Escolar F; Sanjurjo M; Lopez-Fernandez LA

**INSTITUCIÓN / INSTITUTION:** - Servicio de Farmacia, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Doctor Esquerdo 46, 28007, Madrid, España.

**RESUMEN / SUMMARY:** - **PURPOSE:** Oxaliplatin or irinotecan is usually administered jointly with fluoropyrimidines in colorectal cancer patients treated with chemotherapy. Both drugs have different toxicity patterns. Biomarkers for predicting high-risk severe adverse reactions can help select the best treatment. **METHODS:** A retrospective analysis of 106 colorectal cancer patients receiving an oxaliplatin-based treatment and 56 receiving an irinotecan-based treatment was performed. One copy number variant (GSTT1) and nine polymorphisms in irinotecan and oxaliplatin metabolism, transport or DNA repair genes (ABCB1, UGT1A1, XRCC1, ERCC1, ERCC2, GSTP1) were genotyped by SNaPshot, polymerase chain reactions' length fragments, or copy number assays. **RESULTS:** In irinotecan-treated patients, C allele of ABCB1 C1236T SNP was associated with a lower risk of asthenia (OR = 0.043; 96 % CI = 0.004-0.444; P = 0.008) and C allele of ABCB1 C3435T SNP was associated with a lower risk of diarrhea (OR = 0.162; 95 % CI = 0.031-0.844; P = 0.031); and individuals with two copies of GSTT1 gene had a lower risk for asthenia (OR = 0.074; 95 % CI = 0.009-0.617; P = 0.016). In oxaliplatin-treated patients, carriers of two C variants of Asn118Asn ERCC1 SNP had a lower risk for neutropenia (OR = 0.203; 95 % CI = 0.060-0.683; P = 0.01). **CONCLUSIONS:** These biomarkers could help oncologists select the best treatment by reducing toxicity associated with irinotecan or oxaliplatin in colorectal cancer patients, thus increasing their quality of life.

[581]

**TÍTULO / TITLE:** - CDK Inhibitors Induce Mitochondria-Mediated Apoptosis Through The Activation Of Polyamine Catabolic Pathway in LNCaP, DU145 and PC3 Prostate Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Pharm Des. 2013 May 16.

**AUTORES / AUTHORS:** - Arisan ED; Obakan P; Coker-Gurkan A; Calcabrini A; Agostinelli E; Unsal NP

**INSTITUCIÓN / INSTITUTION:** - Istanbul Kultur University, Faculty of Science and Letters, Department of Molecular Biology and Genetics, Istanbul, Turkey.

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**RESUMEN / SUMMARY:** - Androgen signaling is critical in prostate cancer development and progression. The co-existence of hormone responsive and irresponsive cells due to functional androgen receptor (AR) in prostate gland is the major obstacle in prostate cancer therapy models. Targeting aberrant cell cycle by novel cell cycle blocking agents is a promising strategy to treat various types of malignancies. Purvalanol and roscovitine are cyclin dependent kinase (CDK) inhibitors able to activate apoptotic cell death by inducing cell cycle arrest at G1/S and G2/M phases in cancer cells. Polyamines are unique cationic amine derivatives involved in the regulation of cell proliferation. Although the elevated intracellular level of polyamines (putrescine, spermidine and spermine) is typical for prostate gland, abnormal regulation of polyamine metabolism might result in rapid cell proliferation and, thus in prostate cancer progression. Therefore, treatment with drug-induced depletion of intracellular polyamine levels through the activated polyamine catabolism is critical to achieve successful strategies for prostate cancer. In this study we aimed to investigate the apoptotic efficiency of CDK inhibitors in three prostate cancer cell lines (LNCaP, DU145 and PC3), showing different AR expression profile. We found that both purvalanol and roscovitine were able to induce apoptosis at moderate cytotoxic concentrations by decreasing mitochondria membrane potential. The apoptotic effect of both CDK inhibitors was due to activation of caspases by modulating Bcl-2 family members. The efficiency of drugs was quite similar on the three prostate cell lines used in this study. However, DU145 cells were found the least sensitive against CDK inhibitors while purvalanol was more potent than roscovitine. Similarly to classical chemotherapeutic agents, both drugs could up-regulate polyamine catabolic enzymes (SSAT, SMO and PAO) in cell type dependent manner. Transient silencing of SSAT and/or inhibition of PAO/ SMO with MDL72527 prevented CDK inhibitors-induced apoptotic cell death in DU145 and PC3 cells. Although roscovitine was less effective in DU145 cells, pre-treatment with alpha-difluoromethylornithine (DFMO), an inhibitor of ODC, enhanced the roscovitine-induced apoptotic cell death through the cleavage of caspase-9 and caspase-3. Therefore, we conclude that polyamine catabolism might have essential role in the cellular responses against CDK inhibitors in different androgen-responsive or irresponsive prostate cancer cells.

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[582]

**TÍTULO / TITLE:** - Paradoxical effect of lenalidomide on cytokine/growth factor profiles in multiple myeloma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Mar 14;108(9):1801-6. doi: 10.1038/bjc.2013.186. Epub 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1038/bjc.2013.186](http://1038/bjc.2013.186)

**AUTORES / AUTHORS:** - Maiga S; Gomez-Bougie P; Bonnaud S; Gratas C; Moreau P; Le Gouill S; Pellat-Deceunynck C; Amiot M

**INSTITUCIÓN / INSTITUTION:** - 1] Inserm, UMR892, Departement de Recherche en Cancerologie Nantes/Angers, 8, quai Moncoussu, Nantes 44007, France [2] Universite de Nantes, Nantes 44000, France [3] CNRS, UMR 6299, Nantes 44000, France.

**RESUMEN / SUMMARY:** - Background:Lenalidomide is an active immunomodulatory and antiproliferative agent in multiple myeloma. However, the molecular mechanisms driving these activities are not yet fully elucidated. Therefore, we investigated the modulation of the cytokine/growth factor patterns of myeloma cells under LEN treatment.Methods:Lenalidomide effect on myeloma cell proliferation was investigated in a myeloma cell line collection (n=23) by (3)H-thymidine incorporation. Modulation of the cytokine/growth factor patterns of myeloma cells under LEN treatment was analysed by real-time quantitative PCR.Results:Lenalidomide inhibits the proliferation of two-thirds of myeloma cell lines independently of their genetic background. We demonstrated that LEN increased TNF-alpha and IL-8 inflammatory cytokines and insulin-like growth factor-1 (IGF-1) growth factor in both sensitive and resistant myeloma cells to LEN.Conclusion:Lenalidomide favours a uniform TNF-alpha and IL-8 inflammatory and IGF-1 secretory profile of myeloma cells, an observation that raises important questions for therapeutic approaches incorporating the agent.

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[583]

**TÍTULO / TITLE:** - Long-term follow-up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Haematologica. 2013 May 3.

●●Enlace al texto completo (gratis o de pago)

[3324/haematol.2012.082412](#)

**AUTORES / AUTHORS:** - Bachy E; Houot R; Morschhauser F; Sonet A; Brice P; Belhadj K; Cartron G; Audhuy B; Ferme C; Feugier P; Sebban C; Delwail V; Maisonneuve H; Le Gouill S; Lefort S; Brousse N; Foussard C; Salles G

**INSTITUCIÓN / INSTITUTION:** - France;

**RESUMEN / SUMMARY:** - Anti-CD20-containing chemotherapy regimens have become the standard of care for patients with follicular lymphoma needing cytotoxic therapy. Four randomized trials demonstrated a clinical benefit for patients treated with rituximab. However, no long-term follow-up (ie > 5 years) of these trials is yet available. Between May 2000 and May 2002, 358 newly diagnosed patients with high-tumor burden follicular lymphoma were randomized to receive cyclophosphamide, adriamycin, etoposide and prednisolone plus interferon-alpha2a or a similar chemotherapy-based regimen plus rituximab and outcome was updated. With a median follow-up of 8.3

years, addition of rituximab remained significantly associated with prolonged event-free survival (primary endpoint) ( $P=0.0004$ ) with a trend towards a benefit for overall survival ( $P=0.076$ ). The Follicular Lymphoma International Prognostic Index score was strongly associated with outcome for both event-free and overall survival in univariate analysis and its prognostic value remained highly significant after adjusting for other significant covariates in multivariate models ( $P<0.0001$  and  $P=0.001$  respectively). Considering long-term toxicity, the addition of rituximab in first line setting was confirmed as safe with regards to secondary malignancies development. Long-term follow-up of patients with follicular lymphoma treated in the FL2000 study confirms the sustained clinical benefit of rituximab without long-term toxicity. This study was registered at ClinicalTrials.gov number NCT00136552.

[584]

**TÍTULO / TITLE:** - The suppression of thoc1 in cancer cell apoptosis mediated by activated macrophages is nitric oxide-dependent.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Pharmacol. 2013 May 17. pii: S0006-2952(13)00293-1. doi: 10.1016/j.bcp.2013.05.009.

●●Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.05.009](http://1016/j.bcp.2013.05.009)

**AUTORES / AUTHORS:** - Lin YS; Lin CH; Huang LD; Chao T; Kuo CD; Hung LC; Wong FH; Lin CC; Fu SL

**INSTITUCIÓN / INSTITUTION:** - Institute of Public Health, National Yang-Ming University, Taipei 11221, Taiwan; Program in Molecular Medicine, National Yang-Ming University and Academia Sinica, Taipei 11221, Taiwan.

**RESUMEN / SUMMARY:** - Activation of Toll-like receptor 4 (TLR4) triggers both innate and adaptive immunity. We previously identified a synthetic glycolipid, CCL-34, which can induce anticancer immunity in a TLR4-dependent manner. In the present study, we demonstrated the involvement of THO complex 1 (thoc1) in the CCL-34-induced anticancer mechanism. The expression of thoc1 was suppressed in bladder cancer cells (MBT-2) co-cultured with CCL-34-activated macrophages, whereas treatment with an iNOS inhibitor could restore the expression of thoc1. Direct treatment of MBT-2 cells with an NO donor also repressed thoc1 expression. Importantly, the thoc1-overexpressing MBT-2 cells (MBT/thoc1) exhibited greater resistance than the MBT-2 cells to cytotoxicity induced by the NO donor or the CCL-34-activated macrophages. In addition, treatments with CCL-34-activated macrophages or the NO donor resulted in the suppression of thoc1 promoter activity in MBT-2 cells, and mutations in the antioxidant response element (ARE) of the thoc1 promoter abolished the repression induced by these treatments. Furthermore, NO treatment increased the expression and nuclear localization of nuclear factor E2-related factor 2 (Nrf2) in MBT-2 cells. Overexpression of Nrf2 suppressed thoc1 promoter activity in an ARE-dependent manner, and knock-down of nrf2 reversed the

suppression. Notably, Bcl-2 expression was suppressed in MBT-2 cells, but not in MBT-2/thoc1 cells, treated with CCL-34-activated macrophages or the NO donor. In summary, our results demonstrate that NO-mediated thoc1 downregulation, via Nrf2, is a key step in the cancer cell apoptosis induced by CCL-34-treated macrophages and that downregulated thoc1 could lead to Bcl-2 downregulation and subsequent cancer cell apoptosis.

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[585]

**TÍTULO / TITLE:** - Correlation between Tc-HYNIC-octreotide SPECT/CT somatostatin receptor scintigraphy and pathological grading of meningioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurooncol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1007/s11060-013-1146-](#)

[y](#)

**AUTORES / AUTHORS:** - Wang S; Yang W; Deng J; Zhang J; Ma F; Wang J

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, Xijing Hospital, Fourth Military Medical University, 15 West Changle Road, Xi'an, 710032, Shaanxi, China.

**RESUMEN / SUMMARY:** - The aim of this study was to explore the association of 99mTc-HYNIC-octreotide SPECT/CT somatostatin receptor scintigraphy (SRS) with the pathological grading and expression of somatostatin receptor 2 (SSTR2) for meningioma, and to define possible roles of SRS in the pathological grading of meningioma. Thirty patients with meningiomas diagnosed by MRI and treated with 99mTc-HYNIC-octreotide SPECT/CT SRS. Meningioma tissues were obtained from analyzing pathological grading and measuring the expression of SSTR2 with immunohistochemical staining. The meningioma side (T) to the contralateral side (NT) ratios (T/TN) of radioactive counts were calculated to investigate their association with the pathological grading of meningioma and the expression of SSTR2. All 30 cases showed high meningioma radioactivity accumulation using SRS with a sensitivity of 100 %, while CT scans only detected 25 cases with a sensitivity of 83 %. Twenty cases with grade I meningioma had a T/NT ratio of 3.80 +/- 1.67, which was significantly lower than the other 10 cases (9.57 +/- 3.78) with a grade II meningioma (P < 0.01). All meningiomas expressed SSTR2 as detected by immunohistochemical staining, and the T/NT ratio was positively associated with the pathological grading of meningioma and the expression of SSTR2 (with r of 0.784 and 0.805, respectively). 99mTc-HYNIC-octreotide SPECT/CT SRS is a sensitive technique for detecting meningioma, and the T/NT ratio of the SRS data closely correlates with the pathological grade of meningioma and the expression of SSTR2.

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[586]

**TÍTULO / TITLE:** - Expression of metallothionein-1 and metallothionein-2 as a prognostic marker in hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gastroenterol Hepatol. 2013 May 10. doi: 10.1111/jgh.12261.

●●Enlace al texto completo (gratis o de pago) [1111/jgh.12261](#)

**AUTORES / AUTHORS:** - Park Y; Yu E

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - BACKGROUND AND AIMS: Metallothioneins (MTs) -1 and -2 are a group of low-molecular weight, cysteine-rich, intracellular metal binding proteins that are involved in diverse functions such as metal homeostasis, cell cycle progression, cell differentiation and carcinogenesis. This study investigated the expression of MT-1 and MT-2 as a prognostic marker in hepatocellular carcinoma (HCC). METHODS: A total of 370 HCCs, 336 adjacent non-cancerous livers, and 12 normal livers were evaluated for the expression of MT-1 and MT-2 by immunohistochemical staining on tissue microarray. The relationship between the expression of MT-1 and MT-2 and the clinicopathological parameters of HCC was assessed. RESULTS: The expression of MT-1 and MT-2 was uniformly strong in nucleus and cytoplasm in normal liver, whereas it was variable in non-cancerous livers and HCCs. The loss of nuclear and cytoplasmic expression of MT-1 and MT-2 was significantly frequent in HCCs compared with the adjacent noncancerous livers ( $p < 0.001$ ). The loss of nuclear expression of MT-1 and MT-2 was significantly correlated with high Edmondson-Steiner grade and the presence of microscopic vascular invasion ( $p < 0.05$ ). In multivariate analysis, the loss of nuclear MT-1 and MT-2 expression was identified as an independent poor prognostic factor for both recurrence free survival and overall survival. CONCLUSIONS: The expression of MT-1 and MT-2 may play a role in differentiation and carcinogenesis, and can be used as a useful predictor of prognosis in HCC.

[587]

**TÍTULO / TITLE:** - p42.3: A promising biomarker for the progression and prognosis of human colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1007/s00432-013-1434-0](#)

**AUTORES / AUTHORS:** - Yuan XS; Zhang Y; Guan XY; Dong B; Zhao M; Mao LL; Lu YY; Tian XY; Hao CY

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Hepato-Pancreato-Biliary Surgery, Peking University School of Oncology, Peking

University Cancer Hospital and Institute, 52 Fucheng Rd, Haidian District, Beijing, 100142, China.

**RESUMEN / SUMMARY:** - PURPOSE: As a novel cell cycle-related gene, p42.3 has been shown to play a key role in the cell proliferation and tumorigenicity of gastric cancer. To date, the association between p42.3 and colorectal cancer (CRC) has not been reported. This study investigated the expression of p42.3 and its potential role in human colorectal cancers. METHODS: Real-time polymerase chain reaction and western blotting were used to evaluate p42.3 mRNA and protein expression in 14 pairs of fresh frozen CRC samples, matched with adjacent normal mucosa. The p42.3 protein was evaluated by immunohistochemistry using CRC tissue microarrays, which included 212 CRC specimens and corresponding normal colorectal mucosa. The expression profiles of p42.3 in CRC tissues were analyzed against clinicopathological factors and post-surgical survival status. The expression profiles of p42.3 were also investigated in six human colon carcinoma cell lines. RESULTS: p42.3 was demonstrated to be over-expressed in colorectal cancer tissues compared with normal mucosa in the 14 tissue pairs ( $P = 0.011$ ) and was significantly higher in patients with poor tumor differentiation ( $P = 0.045$ ); patients positive for p42.3 expression had a poorer prognosis than those not expressing this protein ( $P = 0.033$ ). In a multivariate survival analysis, p42.3 expression was identified as an independent prognostic factor for CRC patients ( $P = 0.030$ ). CONCLUSIONS: The results indicated that p42.3 might play an important role in the progression of CRC, and it has a great value for assessing CRC patient prognosis after surgery.

[588]

**TÍTULO / TITLE:** - Synthesis and in vitro cytotoxicity of andrographolide-19-oic acid analogues as anti-cancer agents.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Jun 1;23(11):3166-9. doi: 10.1016/j.bmcl.2013.04.010. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.04.010](http://1016/j.bmcl.2013.04.010)

**AUTORES / AUTHORS:** - Chen D; Song Y; Lu Y; Xue X

**INSTITUCIÓN / INSTITUTION:** - Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China.

**RESUMEN / SUMMARY:** - The synthesis of a series of andrographolide-19-oic acid derivatives was described and their in vitro anti-tumor activity against two human cell lines was evaluated. Most compounds were found to exhibit significant cytotoxicity, better than andrographolide, and compounds 9d and 9b were identified as the most potent with IC<sub>50</sub> values of 1.18 and 6.28 μM against HCT-116 and MCF-7 cell lines, respectively. The preliminary results indicated that the oxidation of C-19-hydroxyl group of andrographolide to corresponding carboxyl group and the subsequent esterification of the formed

carboxylic acid led to considerable improvement in cytotoxicity against the cancer cells.

[589]

**TÍTULO / TITLE:** - The activity of atorvastatin and rosiglitazone on CD38, ZAP70 and apoptosis in lymphocytes of B-cell chronic lymphocytic leukemia in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):603. doi: 10.1007/s12032-013-0603-y. Epub 2013 May 19.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0603-](#)

[y](#)

**AUTORES / AUTHORS:** - Yavasoglu I; Sargin G; Kadikoylu G; Karul A; Bolaman Z  
**INSTITUCIÓN / INSTITUTION:** - Division of Hematology, Adnan Menderes University Medical Faculty, Aydin, Turkey, [dr\\_yavas@yahoo.com](mailto:dr_yavas@yahoo.com).

**RESUMEN / SUMMARY:** - There are a number of studies about the effects of statins and thiazolidinediones on lymphocytes. However, there is no study about possible effects of atorvastatin and rosiglitazone on lymphocytes in patients with chronic lymphocytic leukemia (CLL). We aimed to investigate the effects of atorvastatin and rosiglitazone on CD38, ZAP-70, Annexin V and bcl-2 in lymphocytes of CLL in vitro. Seven (4 males and 3 females) patients with CLL with average age of 56 +/- 8 years were enrolled to the study. The mean values of laboratory tests were as follows: hemoglobin: 12 +/- 1.8 g/dl; hematocrit: %35 +/- 6; platelet count: 156,000 +/- 68,000/mm(3); leukocyte count: 50,500 +/- 38,700/mm(3); and lymphocyte count: 45,700 +/- 38,100/mm(3). The study was performed in three cell cultures groups. Mononuclear cells of blood samples from peripheral veins were separated by Ficoll method. On culture plate with 24 wells, it was suspended with 2 ml RPMI 1640. Then, the plates were incubated in %5 CO2 at 37 degrees C for 24 h. 5 muM atorvastatin-calcium was given to first group, 2 muM rosiglitazone maleate was given to second group, and the third group was included in the study as control group. After 24 h, the expressions of CD5, CD38, ZAP-70 and Annexin V by using flow cytometry with EPICS XL-MCL and the levels of bcl-2 by using ELISA method were re-evaluated. Two-paired Student's t test was used for comparison of the results, and p < 0.05 was accepted as a significance level. While atorvastatin and rosiglitazone did not affect the expression of CD38 and the level of bcl-2, these drugs significantly increased the level of Annexin V when compared with control group (p < 0.001). Both drugs significantly decreased the expressions of CD5 (p = 0.03) and ZAP-70 (p < 0.05) compared with control group. Atorvastatin and rosiglitazone increased apoptosis in lymphocytes of CLL in vitro. Moreover, these drugs decreased the expressions of CD5 and ZAP-70. These drugs must be studied in more detail in the pathogenesis and treatment for CLL.

[590]

**TÍTULO / TITLE:** - miR-421 induces cell proliferation and apoptosis resistance in human nasopharyngeal carcinoma via downregulation of FOXO4.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 23. pii: S0006-291X(13)00848-6. doi: 10.1016/j.bbrc.2013.05.056.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.056](http://1016/j.bbrc.2013.05.056)

**AUTORES / AUTHORS:** - Chen L; Tang Y; Wang J; Yan Z; Xu R

**INSTITUCIÓN / INSTITUTION:** - Neurosurgery Institute, Key Laboratory on Brain Function Repair and Regeneration of Guangdong, Zhujiang Hospital of Southern Medical University, Guangzhou 510282, China; Department of Otolaryngology, Guangzhou General Hospital of PLA Guangzhou Command, Guangzhou 510010, China.

**RESUMEN / SUMMARY:** - microRNAs have been demonstrated to play important roles in cancer development and progression. Hence, identifying functional microRNAs and better understanding of the underlying molecular mechanisms would provide new clues for the development of targeted cancer therapies. Herein, we reported that a microRNA, miR-421 played an oncogenic role in nasopharyngeal carcinoma. Upregulation of miR-421 induced, whereas inhibition of miR-421 repressed cell proliferation and apoptosis resistance. Furthermore, we found that upregulation of miR-421 inhibited forkhead box protein O4 (FOXO4) signaling pathway following downregulation of p21, p27, Bim and FASL expression by directly targeting FOXO4 3'UTR. Additionally, we demonstrated that FOXO4 expression is critical for miR-421-induced cell growth and apoptosis resistance. Taken together, our findings not only suggest that miR-421 promotes nasopharyngeal carcinoma cell proliferation and anti-apoptosis, but also uncover a novel regulatory mechanism for inactivation of FOXO4 in nasopharyngeal carcinoma.

[591]

**TÍTULO / TITLE:** - Spinal astrocytes stimulated by tumor necrosis factor-alpha and/or interferon-gamma attenuate connexin 43-gap junction via c-jun terminal kinase activity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurosci Res. 2013 Jun;91(6):745-56. doi: 10.1002/jnr.23213. Epub 2013 Mar 29.

●●Enlace al texto completo (gratis o de pago) [1002/jnr.23213](http://1002/jnr.23213)

**AUTORES / AUTHORS:** - Zhang FF; Morioka N; Nakashima-Hisaoka K; Nakata Y

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.

**RESUMEN / SUMMARY:** - Spinal astrocytes have important mechanistic contributions to the initiation and maintenance of neurodegenerative diseases

and chronic pain. Under inflammatory conditions, spinal astrocytes are exposed to cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma), and these cytokines could alter astrocytic function by modulating connexin (Cx43), subunits that form channels that modulate intercellular communication in astrocytes. The current study investigated the alteration of Cx43-gap junction in rat primary cultured spinal astrocytes stimulated with cytokines by real-time PCR and Western blotting. The transcriptional and translational levels of Cx43 were significantly but partially reduced 24 and 48 hr treatment with either TNF-alpha (10 ng/ml) or IFN-gamma (5 ng/ml). A mixture of TNF-alpha and IFN-gamma led to a robust decrease of Cx43 expression and, moreover, a moderate reduction of gap junction intercellular communication (GJIC), which was evaluated by a scrap loading/dye transfer assay. Both the decrease of Cx43 expression and the reduction in GJIC induced by the mixture of TNF-alpha and IFN-gamma were prevented by blocking c-jun terminal kinase (JNK) but not by blocking extracellular signaling molecules ERK and p38 kinase, indicating a specific role of astrocytic JNK in the response to cytokines. In addition, treatment with cytokines potently induced the phosphorylation of JNK and c-jun in a time-dependent manner. These results indicate that intercellular communication of astrocytes is significantly disrupted in the inflammatory state and that stimulation of spinal astrocytes with inflammatory cytokines leads to significant inhibition of Cx43-GJIC through activation of the JNK signaling pathway.

[592]

**TÍTULO / TITLE:** - Intracisternal administration of SB203580, a p38 mitogen-activated protein kinase inhibitor, attenuates cerebral vasospasm via inhibition of tumor-necrosis factor-alpha.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Neurosci. 2013 May;20(5):726-30. doi: 10.1016/j.jocn.2012.09.012. Epub 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago) [1016/j.jocn.2012.09.012](http://1016/j.jocn.2012.09.012)

**AUTORES / AUTHORS:** - Pan YX; Chen KF; Lin YX; Wu W; Zhou XM; Zhang XS; Zhang X; Shi JX

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Jinling Hospital, School of Medicine, Nanjing University, 305 East Zhongshan Road, Nanjing 210002, Jiangsu, China.

**RESUMEN / SUMMARY:** - Tumor-necrosis factor-alpha (TNF-alpha) is critical to the development of cerebral vasospasm after subarachnoid hemorrhage (SAH). Hence, therapeutic strategies targeting TNF-alpha can attenuate cerebral vasospasm. This study investigated the effects of SB203580, a p38 mitogen-activated protein kinase (MAPK) inhibitor, on TNF-alpha concentration in the cerebral arteries and the cerebrospinal fluid (CSF) after SAH and on subsequent cerebral vasospasm. Twenty-three rabbits were divided into four

groups: (i) control (without SAH), (ii) SAH (SAH only), (iii) dimethylsulfoxide (DMSO, vehicle), and (iv) SB203580. The severity of vasospasm and the immunoreactivities of TNF-alpha and phosphorylated p38 MAPK in the brain vessels were determined in all animals, and the concentrations of TNF-alpha in the CSF were also assessed. Severe vasospasm was observed in the rabbits from the SAH and DMSO groups. SB203580 reversed vasospasm after SAH. Lower immunoreactivities of TNF-alpha and phosphorylated p38 MAPK were found in the basilar artery in the SB203580 group than in the DMSO group. The concentration of TNF-alpha in the CSF increased after SAH, but treatment with SB203080 after SAH suppressed this increase. Our data show that SB203580 reversed cerebral vasospasm by inhibiting the phosphorylation of p38 MAPK in the basilar artery and by suppressing the increase in TNF-alpha in the basilar artery and CSF after SAH. SB203580 could therefore potentially be used for the treatment of cerebral vasospasm after SAH.

[593]

**TÍTULO / TITLE:** - Oncogene GAEC1 regulates CAPN10 expression which predicts survival in esophageal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Gastroenterol. 2013 May 14;19(18):2772-80. doi: 10.3748/wjg.v19.i18.2772.

●●Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i18.2772](#)

**AUTORES / AUTHORS:** - Chan D; Tsoi MY; Liu CD; Chan SH; Law SY; Chan KW; Chan YP; Gopalan V; Lam AK; Tang JC

**INSTITUCIÓN / INSTITUTION:** - Dessy Chan, Miriam Yuen-Tung Tsoi, Christina Di Liu, Sau-Hing Chan, Johnny Cheuk-On Tang, State Key Laboratory of Chirosciences, Lo Ka Chung Centre for Natural Anti-cancer Drug Development, Department of Applied Biology and Chemical Technology, the Hong Kong Polytechnic University, Hong Kong, China.

**RESUMEN / SUMMARY:** - AIM: To identify the downstream regulated genes of GAEC1 oncogene in esophageal squamous cell carcinoma and their clinicopathological significance. METHODS: The anti-proliferative effect of knocking down the expression of GAEC1 oncogene was studied by using the RNA interference (RNAi) approach through transfecting the GAEC1-overexpressed esophageal carcinoma cell line KYSE150 with the pSilencer vector cloned with a GAEC1-targeted sequence, followed by MTS cell proliferation assay and cell cycle analysis using flow cytometry. RNA was then extracted from the parental, pSilencer-GAEC1-targeted sequence transfected and pSilencer negative control vector transfected KYSE150 cells for further analysis of different patterns in gene expression. Genes differentially expressed with suppressed GAEC1 expression were then determined using Human Genome U133 Plus 2.0 cDNA microarray analysis by comparing with the parental cells and normalized with the pSilencer negative control vector

transfected cells. The most prominently regulated genes were then studied by immunohistochemical staining using tissue microarrays to determine their clinicopathological correlations in esophageal squamous cell carcinoma by statistical analyses. RESULTS: The RNAi approach of knocking down gene expression showed the effective suppression of GAEC1 expression in esophageal squamous cell carcinoma cell line KYSE150 that resulted in the inhibition of cell proliferation and increase of apoptotic population. cDNA microarray analysis for identifying differentially expressed genes detected the greatest levels of downregulation of calpain 10 (CAPN10) and upregulation of trinucleotide repeat containing 6C (TNRC6C) transcripts when GAEC1 expression was suppressed. At the tissue level, the high level expression of calpain 10 protein was significantly associated with longer patient survival (month) of esophageal squamous cell carcinoma compared to the patients with low level of calpain 10 expression (37.73 +/- 16.33 vs 12.62 +/- 12.44, P = 0.032). No significant correlation was observed among the TNRC6C protein expression level and the clinicopathological features of esophageal squamous cell carcinoma. CONCLUSION: GAEC1 regulates the expression of CAPN10 and TNRC6C downstream. Calpain 10 expression is a potential prognostic marker in patients with esophageal squamous cell carcinoma.

[594]

**TÍTULO / TITLE:** - beta-Catenin overexpression is associated with gefitinib resistance in non-small cell lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pulm Pharmacol Ther. 2013 May 23. pii: S1094-5539(13)00123-5. doi: 10.1016/j.pupt.2013.05.005.

●●Enlace al texto completo (gratis o de pago) [1016/j.pupt.2013.05.005](http://1016/j.pupt.2013.05.005)

**AUTORES / AUTHORS:** - Fang X; Gu P; Zhou C; Liang A; Ren S; Liu F; Zeng Y; Wu Y; Zhao Y; Huang B; Zhang Z; Yi X

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Tongji Hospital, Tongji University School of Medicine, Shanghai 200065, China. Electronic address: [dilay\\_123@yahoo.cn](mailto:dilay_123@yahoo.cn).

**RESUMEN / SUMMARY:** - BACKGROUND: Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) presents great challenges in the treatment of non-small cell lung cancer (NSCLC) patients, while the mechanisms are still not well understood. The beta-catenin signaling pathway has been found to be associated with chemoresistance and can activate the EGFR and its downstream pathways. This study aimed to investigate the role of beta-catenin in acquired resistance to EGFR-TKIs in NSCLC cell lines. METHODS: The expression and transcriptional activity of beta-catenin were measured in both the NSCLC cell line PC9 and its sub-line PC9/AB2 which has acquired resistance to gefitinib. Knockdown and overexpression of beta-catenin in the PC9/AB2 and PC9 cells were performed.

The cell survival rate and the activation of the EGFR and its downstream pathways were detected in the two cell lines after transfection. RESULTS: Nuclear translocation of beta-catenin was increased in the PC9/AB2 cells and the baseline expression of members of the beta-catenin signaling pathway was also higher in the PC9/AB2 cells. Knocking down the expression of beta-catenin increased the sensitivity of the PC9/AB2 cells to gefitinib by blocking the activation of the EGFR and its downstream pathways, while beta-catenin overexpression improved PC9 cells resistance to gefitinib by enhancing the activation of the EGFR and its downstream signaling. CONCLUSION: beta-catenin plays an important role in acquired resistance to EGFR-TKIs in NSCLC cell lines and may be a potential therapeutic target for NSCLC patients who have failed to respond to targeted therapy.

[595]

**TÍTULO / TITLE:** - An Updated Systematic Review and Meta-Analysis of the Predictive Value of Serum Biomarkers in the Assessment of Fever during Neutropenia in Children with Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Pediatr Infect Dis J.* 2013 May 13.

●●Enlace al texto completo (gratis o de pago)

[1097/INF.0b013e31829ae38d](#)

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**INSTITUCIÓN / INSTITUTION:** - 1 Children's Cancer Centre, Royal Children's Hospital Melbourne, Parkville, Australia; 2 Department of Infectious Diseases and Infection Control, Peter MacCallum Cancer Centre, East Melbourne, Australia; 3 Department of Pediatrics, Pediatric Oncology Institute (IOP-GRAACC), Federal University of Sao Paulo, Sao Paulo, UNIFESP-Brazil; 4 Centre for Reviews and Dissemination, Alcuin College, University of York, York, YO10 5DD UK; 5 Regional Department of Paediatric Haematology/Oncology, Leeds Teaching Hospitals Trust, Leeds, LS1 3EXUK.

**RESUMEN / SUMMARY:** - BACKGROUND:: Fever during neutropenia (FN) is a frequent and potentially life-threatening complication of the treatment of childhood cancer. The role of biomarkers in predicting morbidity and mortality associated with FN in children has been explored with varying results. This systematic review identified, critically appraised, and synthesised information on the use of biomarkers for the prediction of outcome of FNP in children/young adults, updating a review of initial assessment, and adding further analysis of their value at reassessment. METHODS:: This review was conducted in accordance with the Centre for Reviews and Dissemination Methods, using three different random-effects meta-analysis models. RESULTS:: 37 studies involving over 4689 episodes of FN in children were assessed, including an additional 13 studies investigating 18 biomarkers in 1670 FN episodes since the original review. Meta-analysis was possible for admission C-reactive protein

(CRP), procalcitonin (PCT), interleukin-6 (IL-6) and interleukin-8 (IL-8) in their ability to detect significant infection. Marked heterogeneity exists, precluding clear clinical interpretation of the results. Qualitative synthesis of the role of serial biomarkers suggests their predictive ability may be more pronounced at 24 to 48 hours compared to admission. Direct comparisons of the discriminatory power of admission values of PCT and CRP showed PCT generally had a better discriminatory estimate of serious infection than CRP. CONCLUSIONS:: There remains a paucity of robust and reproducible data on the use of biomarkers in prediction of serious infection in children with FNP. Available evidence suggests PCT has better discriminatory ability than CRP and that the role of serial biomarkers warrants further study.

[596]

**TÍTULO / TITLE:** - Targetting cancer with Ru(III/II)-phosphodiesterase inhibitor adducts: A novel approach in the treatment of cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Hypotheses. 2013 Jun;80(6):841-6. doi: 10.1016/j.mehy.2013.03.029. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago)

[1016/j.mehy.2013.03.029](#)

**AUTORES / AUTHORS:** - Koiri RK; Mehrotra A; Trigun SK

**INSTITUCIÓN / INSTITUTION:** - Biochemistry and Molecular Biology Lab, Department of Zoology, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India. Electronic address: [rajkumarfrombhu@yahoo.com](mailto:rajkumarfrombhu@yahoo.com).

**RESUMEN / SUMMARY:** - Lack of specificity and normal tissue toxicity are the two major limitations faced with most of the anticancer agents in current use. Due to effective biodistribution and multimodal cellular actions, during recent past, ruthenium complexes have drawn much attention as next generation anticancer agents. This is because metal center of ruthenium (Ru) effectively binds with the serum transferrin and due to higher concentration of transferrin receptors on the tumor cells, much of the circulating Ru-transferrin complexes are delivered preferentially to the tumor site. This enables Ru-complexes to become tumor cell specific and to execute their anticancer activities in a somewhat targeted manner. Also, there are evidences to suggest that inhibition of phosphodiesterases leads to increased cyclic guanosine monophosphate (cGMP) level, which in turn can evoke cell cycle arrest and can induce apoptosis in the tumor cells. In addition, phosphodiesterase inhibition led increased cGMP level may act as a potent vasodilator and thus, it is likely to enhance blood flow to the growing tumors in vivo, and thereby it can further facilitate delivery of the drugs/compounds to the tumor site. Therefore, it is hypothesized that tagging PDE inhibitors (PDEis) with Ru-complexes could be a relevant strategy to deliver Ru-complexes-PDEi adduct preferentially to the tumor site. The Ru-complex tagged entry of PDEi is speculated to initially

enable the tumor cells to become a preferential recipient of such adducts followed by induction of antitumor activities shown by both, the Ru-complex & the PDEi, resulting into enhanced antitumor activities with a possibility of minimum normal tissue toxicity due to administration of such complexes.

[597]

**TÍTULO / TITLE:** - Prognostication of OCT4 isoform expression in prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0817-9](http://1007/s13277-013-0817-9)

**AUTORES / AUTHORS:** - de Resende MF; Chinen LT; Vieira S; Jampietro J; da Fonseca FP; Vassallo J; Campos LC; Guimaraes GC; Soares FA; Rocha RM

**INSTITUCIÓN / INSTITUTION:** - Department of Anatomic Pathology, A.C. Camargo Cancer Hospital, Rua Professor Antonio Prudente 211, Liberdade, Sao Paulo, SP, 01509-900, Brazil.

**RESUMEN / SUMMARY:** - Cancer stem cells (CSCs) refer to a subset of tumor cells that self-renew and affect tumor heterogeneity. This model has attracted considerable interest in recent years due to its implications in the prognosis and clinical management of cancer because CSCs mediate the occurrence, growth, and recurrence of tumors. OCT4 is central to embryonic stem cell self-renewal and differentiation into specific lineages and encodes two chief isoforms that are generated by alternative splicing-OCT4A and OCT4B. Their function in prostate cancer (PCa) is unknown. The prognostic function of OCT4 isoforms in PCa samples was examined by immunohistochemistry (IHC) and sensitivity and specificity of the antibodies used were evaluated by molecular biology techniques. Biochemical and pathological data and specimens from 193 patients with PCa were evaluated retrospectively. IHC, western blot, immunofluorescence, and automated image analysis were also performed. IHC was performed on a tissue microarray, and western blot and immunofluorescence were performed using the PCa cell line DU-145. IHC expression of OCT4 isoforms correlated with biochemical and pathological parameters, particularly biochemical recurrence-free survival (BCRFS). Patients with higher levels of OCT4B had lower Gleason scores and decreased likelihood of experiencing biochemical recurrence (BR). OCT4A+ OCT4B- patients had the shortest BCRFS, and positivity for OCT4B expression was an independent prognostic factor for BCRFS in the multivariate analysis. We conclude that the expression of OCT4B is a strong marker of good prognosis, and its presence is associated with a decreased likelihood of BR. Thus, OCT4B might represent a powerful clinical prognostic biomarker for PCa patients.

[598]

**TÍTULO / TITLE:** - Serum transferrin as a predictor of prognosis for hepatic arterial infusion chemotherapy in advanced hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatol Res. 2013 Apr 22. doi: 10.1111/hepr.12141.

●●Enlace al texto completo (gratis o de pago) [1111/hepr.12141](#)

**AUTORES / AUTHORS:** - Zaitu J; Yamasaki T; Saeki I; Harima Y; Iwamoto T; Harima Y; Matsumoto T; Urata Y; Hidaka I; Marumoto Y; Ishikawa T; Takami T; Yamamoto N; Kaino S; Uchida K; Terai S; Sakaida I

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Ube, Japan.

**RESUMEN / SUMMARY:** - AIM: We recently reported that the iron chelator deferoxamine (DFO) is efficacious in advanced hepatocellular carcinoma (HCC) patients. Iron regulation may thus have an important impact in HCC therapy. Because transferrin is a native chelator that regulates iron homeostasis, it may act as an anticancer agent in a similar manner as DFO. The objective of this study was to evaluate serum transferrin as a prognostic predictor in advanced HCC patients undergoing hepatic arterial infusion chemotherapy (HAIC). METHODS: We retrospectively studied 44 patients receiving HAIC and analyzed various parameters for their possible use as prognostic predictors. RESULTS: The 1-, 2- and 3-year cumulative survival rates were 36.4%, 18.2% and 8.5%, respectively, and the median survival time (MST) was 7.0 months. The survival rates of patients who had serum transferrin of 190 mg/dL or more (MST, 12.0 months) were significantly better than those of patients who had serum transferrin of less than 190 mg/dL (MST, 4.9 months). Multivariate analysis identified serum transferrin of 190 mg/dL or more (hazard ratio [HR], 0.282; 95% confidence interval [CI], 0.132-0.603; P = 0.001) and Child-Pugh score B (HR, 1.956; 95% CI, 1.034-3.700; P = 0.039) as independent prognostic predictors. There was a significant correlation between serum transferrin level and therapeutic effect (P < 0.001). CONCLUSION: Serum transferrin could be useful as a prognostic predictor in advanced HCC patients before HAIC treatment.

[599]

**TÍTULO / TITLE:** - Overexpression of carbonic anhydrase II and Ki-67 proteins in prognosis of gastrointestinal stromal tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Gastroenterol. 2013 Apr 28;19(16):2473-80. doi: 10.3748/wjg.v19.i16.2473.

●●Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i16.2473](#)

**AUTORES / AUTHORS:** - Liu LC; Xu WT; Wu X; Zhao P; Lv YL; Chen L

**INSTITUCIÓN / INSTITUTION:** - Li-Cheng Liu, Wen-Tong Xu, Xin Wu, Lin Chen, Department of General Surgery, General Hospital of PLA, Beijing 100853, China.

**RESUMEN / SUMMARY:** - AIM: To investigate the expression and prognostic value of carbonic anhydrase II (CA II) and Ki-67 in gastrointestinal stromal tumors (GISTs). METHODS: One hundred and thirteen GIST patients admitted to Chinese People's Liberation Army General Hospital from January 2004 to December 2010 were retrospectively followed up, and immunohistochemistry was used to detect CA II, Ki-67 and CD117 expression in tumor samples. The survival rates of the patients were analyzed using the Kaplan-Meier method. Log-rank test, chi(2) test and Cox proportional hazards model were used to determine the relationships between CA II, Ki-67 and CD117 expression and prognostic value in GISTs. RESULTS: The survival rates at 1, 3 and 5 years were 90.0%, 82.0% and 72.0% in all patients. However, in patients with positive CA II or Ki-67, the survival rates were 92.0%, 83.0% and 77.0% or 83.0%, 66.6% and 53.0%, respectively. Compared with the negative groups, the survival rates in the positive groups were significantly lower (CA II log-rank P = 0.000; Ki-67 log-rank P = 0.004). Multivariate Cox analysis revealed that CA II, CD117 and Ki-67 were considerable immune factors in prognosis of GIST patients (CA II P = 0.043; CD117 P = 0.042; Ki-67 P = 0.007). Besides, tumor diameter, mitotic rate, tumor site, depth of invasion, complete resection, intraoperative rupture, and adjuvant therapy were important prognosis predictive factors. Our study indicated that CA II had strong expression in GISTs and the prognosis of GISTs with high CA II expression was better than that of GISTs with low or no expression, suggesting that CA II is both a diagnostic and prognostic biomarker for GIST. CONCLUSION: CA II and Ki-67 are significant prognostic factors for GISTs. CA II associated with neovascular endothelia could serve as a potential target for cancer therapy.

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[600]

**TÍTULO / TITLE:** - Serum miR-21 and miR-92a as biomarkers in the diagnosis and prognosis of colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 28.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0753-](#)

[8](#)

**AUTORES / AUTHORS:** - Liu GH; Zhou ZG; Chen R; Wang MJ; Zhou B; Li Y; Sun XF

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, 37 Guo Xue Xiang, Chengdu, 610041, China.

**RESUMEN / SUMMARY:** - Previous studies from our laboratory identified a number of miRNAs that were aberrantly expressed in colorectal cancer (CRC)

tissue. However, their diagnostic and prognostic value in serum has not been fully evaluated. In the present study, we measured the levels of five miRNAs (miR-21, miR-31, miR-92a, miR-18a, and miR-106a) in serum samples from 200 CRC patients, 50 advanced adenoma patients, and 80 healthy controls by real-time quantitative polymerase chain reaction (RT-PCR). In our study, the levels of miR-21 and miR-92a in patients with CRC and advanced adenoma were significantly higher than those in healthy controls (all  $P < 0.05$ ). MiR-21 yielded an area under the receiver-operating characteristics (ROC) curve (AUC) of 0.802 and miR-92a yielded an AUC of 0.786 in discriminating CRCs from the controls. Additionally, miR-21 and miR-92a yielded an AUC of 0.709 and 0.701, respectively, in discriminating advanced adenomas from the controls. Combined ROC analyses using both miRNAs, revealed an elevated AUC of 0.847 in discriminating CRCs, and an AUC of 0.722 in discriminating advanced adenomas from the controls. In the multivariate Cox proportional hazards analysis, high miR-92a expression in CRC was independently associated with poor survival ( $P = 0.03$ ; hazard ratio 4.36; 95 % confidence interval = 1.64-11.57). No significant difference was observed in the levels of miR-18a, miR-31, and miR-106a among CRC, advanced adenoma, and control samples. In summary, our data indicate that miR-21 and miR-92a serum levels have potential value for early detection of CRC. Furthermore, miR-92a has prognostic value in CRC patients.

[601]

**TÍTULO / TITLE:** - Mediation of multiple pathways regulating cell proliferation, migration, and apoptosis in the human malignant glioma cell line U87MG via unphosphorylated STAT1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurosurg. 2013 Jun;118(6):1239-47. doi: 10.3171/2013.3.JNS122051. Epub 2013 Apr 19.

●●Enlace al texto completo (gratis o de pago) [3171/2013.3.JNS122051](#)

**AUTORES / AUTHORS:** - Ju H; Li X; Li H; Wang X; Wang H; Li Y; Dou C; Zhao G  
**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, First Bethune Hospital of Jilin University;

**RESUMEN / SUMMARY:** - Object Signal transducer and activator of transcription 1 (STAT1) is thought to be a tumor suppressor protein. The authors investigated the expression and role of STAT1 in glioblastoma. Methods Immunohistochemistry was used to detect the expression of STAT1 in glioblastoma and normal brain tissues. Reverse transcription-polymerase chain reaction and Western blot analysis were used to detect mRNA and protein expression levels of STAT1. Cell growth, proliferation, migration, apoptosis, and the expression of related genes and proteins (Bcl-2, Bax, cleaved caspase-3, caspase-9, p21, and proliferating cell nuclear antigen) were examined in vitro via cell counting kit-8, wound-healing, flow cytometry, Rhodamine B, TUNEL,

and Western blot assays. Results Human glioblastoma had decreased expression of STAT1 proteins. Transfection of the U87MG cells with STAT1 plasmid in vitro demonstrated significant inhibition of cell growth and an increase in apoptotic cell death compared with cells transfected with vector or mock plasmids. These effects were associated with the upregulation of cleaved caspase-3, Bax, and p21 and the downregulation of Bcl-2 expression. Conclusions The results of this study suggest that increased expression of STAT1 by transfection with STAT1 plasmid synergistically inhibits human U87MG glioblastoma cell growth in vitro.

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[602]

**TÍTULO / TITLE:** - Changes of apoptosis in tumor tissues with time after irreversible electroporation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 May 17. pii: S0006-291X(13)00821-8. doi: 10.1016/j.bbrc.2013.05.039.

●●Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.039](http://1016/j.bbrc.2013.05.039)

**AUTORES / AUTHORS:** - Surnamekim GB; Surnamesung GK; Surnamebaik GY; Surnamemoon GW; Surnamekim GS; Surnameyi GH; Surnamejung GH; Surnamemoon GH; Surnamechoi GK

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology and Seoul National University Cancer Research Institute, Seoul National University College of Medicine, SNU-SMG Boramae Medical Center, 39 Boramae-Gil, Dongjak-Gu, Seoul 156-707, Republic of Korea.

**RESUMEN / SUMMARY:** - Irreversible electroporation is a novel method of ablating living tissues through its non-thermal effects, unlike radiofrequency ablation which has a severe problem of heat sink. It is due to high-energy direct current which leads to permanent disruption of lipid bilayer integrity in terms of exchanges between intra- and extracellular components via nano-sized pores. That finally causes irreversible damage to cellular homeostasis. Irreversibly damaged cells may undergo apoptosis followed by necrosis with time after electroporation. This damage can make it possible to monitor the ablated area with time post-IRE through MR imaging and an ultrasound system. Most previous studies have investigated the immediate response of undesired tissue to IRE. In our study, we showed changes of tumor tissues with time post-IRE by histological analysis and MR imaging. Tissues under IRE ablation showed a peak apoptotic rate at 24h after IRE ablation with viable tissues at the peripheral rim of treated tissues in histological analysis. This phenomenon was also observed with no enhancement on contrast-enhanced MR images due to devascularization of IRE ablated zones.

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[603]

**TÍTULO / TITLE:** - Aquaporin 9, a promising predictor for the cytotoxic effects of arsenic trioxide in acute promyelocytic leukemia cell lines and primary blasts.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jun;29(6):2362-8. doi: 10.3892/or.2013.2388. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2388](#)

**AUTORES / AUTHORS:** - Iriyama N; Yuan B; Yoshino Y; Hatta Y; Horikoshi A; Aizawa S; Takeuchi J; Toyoda H

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Rheumatology, Nihon University School of Medicine, Itabashi Hospital, Itabashi-ku, Tokyo 173-8610, Japan.

**RESUMEN / SUMMARY:** - A close correlation between the cytotoxic effects of arsenic trioxide (ATO) and aquaporin-9 (AQP9) expression levels has been proposed, yet detailed studies are still needed to confirm this association. Thus, in the present study, the correlation between the expression levels of AQP9 and sensitivity to ATO was investigated using two acute promyelocytic leukemia (APL) cell lines, NB4 and HT93A, as well as primary APL cells from newly diagnosed and relapsed APL patients. A substantially higher sensitivity to ATO-mediated induction of apoptosis was observed in the NB4 cells when compared to that in the HT93A cells. In addition, markedly higher expression levels of AQP9, as assessed using flow cytometry, along with more intracellular arsenic accumulation, were observed in the NB4 cells. More importantly, similar to APL cell lines, the trend of expression levels of AQP9 correlated closely with the differential sensitivity to ATO-mediated induction of apoptosis in primary APL cells. In contrast, no correlation was observed between ATO sensitivity associated with AQP9 expression levels and the expression profiles of cell surface markers as well as chromosomal alterations. These results provide direct evidence that the expression levels of AQP9, rather than other biomarkers such as cell surface markers and chromosomal alterations, correlate closely with the sensitivity to ATO in both APL cell lines and primary blasts. These findings suggest that the AQP9 expression status of APL patients is a predictive marker for the successful outcome of ATO treatment, since AQP9 plays a pivotal role in various arsenite-mediated biological effects on normal and cancer cells. Moreover, flow cytometry may be a new convenient and valuable tool for analyzing the AQP9 status of APL patients compared to current methods such as western blotting.

[604]

**TÍTULO / TITLE:** - Glypican-3 is a potential prognostic biomarker for hepatocellular carcinoma after curative resection.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Surgery. 2013 Apr 16. pii: S0039-6060(13)00066-4. doi: 10.1016/j.surg.2013.02.014.

●●Enlace al texto completo (gratis o de pago) [1016/j.surg.2013.02.014](http://1016/j.surg.2013.02.014)

**AUTORES / AUTHORS:** - Fu SJ; Qi CY; Xiao WK; Li SQ; Peng BG; Liang LJ

**INSTITUCIÓN / INSTITUTION:** - Department of Hepatobiliary Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Glypican-3 (GPC3), an oncofetal protein, is overexpressed in hepatocellular carcinoma (HCC). The diagnostic efficacy of GPC3 for HCC has been evaluated intensively in recent years; however, the prognostic value of GPC3 for HCC has not been well clarified. The purpose of this study was to investigate the relationship between GPC3 and postoperative patient survival in a prospective database. METHODS: GPC3 protein was detected by immunohistochemistry. The relationship between GPC3 expression level and patients' clinicopathologic factors was analyzed. Kaplan-Meier survival analysis was used to calculate patients' survival and was compared by using the log rank test. The Cox regression model was used to identify the risk factors associated with prognosis. RESULTS: GPC3 was expressed in 84% of HCC tissues. GPC3 protein expression was correlated with the number of tumors ( $P = .015$ ), serum alpha-fetoprotein (AFP) level ( $P = .011$ ), and TNM stage ( $P = .006$ ). High GPC3 expression was an independent risk factor for poor postoperative disease-free survival (hazard ratio [HR] = 0.469; 95% confidence interval [CI] 0.303-0.727;  $P = .001$ ); and overall survival (HR = 0.435; 95% CI, 0.257-0.736;  $P = .002$ ). Stratification analysis indicated that GPC3 had a good predictive value for tumor recurrence in patients with HCC who have normal serum AFP levels. Also, GPC3 expression status could predict the outcomes of patients with stage I disease. CONCLUSION: GPC3 is a potential and reliable biomarker for predicting tumor recurrence and overall survival in HCC patients after curative resection.

[605]

**TÍTULO / TITLE:** - Infliximab counteracts tumor necrosis factor-alpha-enhanced induction of matrix metalloproteinases that degrade claudin and occludin in non-pigmented ciliary epithelium.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochem Pharmacol. 2013 Apr 16. pii: S0006-2952(13)00230-X. doi: 10.1016/j.bcp.2013.04.006.

●●Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.04.006](http://1016/j.bcp.2013.04.006)

**AUTORES / AUTHORS:** - Yamada H; Yoneda M; Inaguma S; Watanabe D; Banno S; Yoshikawa K; Mizutani K; Iwaki M; Zako M

**INSTITUCIÓN / INSTITUTION:** - Department of Ophthalmology, Aichi Medical University, Aichi, Japan.

**RESUMEN / SUMMARY:** - Infliximab, a monoclonal antibody directed against human tumor necrosis factor-alpha (TNF-alpha), effectively treats anterior uveitis, which can accompany Behcet's disease. Here, we investigated the underlying mechanism of this action. We examined human, non-pigmented

ciliary epithelial cells (HNPCECs), which make up the blood-aqueous barrier (BAB) in the uvea. We measured the expression levels of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in the presence or absence of TNF-alpha using quantitative, real-time polymerase chain reaction and enzyme-linked immunosorbent assays. The expression of MMP-1, MMP-3, and MMP-9 increased in the presence of TNF-alpha, and the addition of infliximab reversed the increase. The TNF-alpha effects were more attenuated when infliximab was added before than when it was added after TNF-alpha exposure. Gelatin zymography demonstrated that the protease activity of these MMPs was also increased in the presence of TNF-alpha and attenuated with infliximab. Immunostaining showed that MMP-1, MMP-3, and MMP-9 degraded claudin-1 and occludin in HNPCECs and in non-pigmented ciliary epithelial cells of the swine ciliary body. In a monolayer of HNPCECs, we found that permeability was significantly increased with MMP treatment. Thus, TNF-alpha increased levels of MMPs in cells that form the BAB, and MMPs degraded components of the tight junctions in the BAB, which increased permeability through the cellular barrier. Furthermore, infliximab effectively attenuated the TNF-alpha-induced increases in MMP expression in cells that make up the BAB. These findings might suggest a basis for the clinical prevention of anterior uveitis.

[606]

**TÍTULO / TITLE:** - MSH3 expression does not influence the sensitivity of colon cancer HCT116 cell line to oxaliplatin and poly(ADP-ribose) polymerase (PARP) inhibitor as monotherapy or in combination.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [1007/s00280-013-2175-](http://1007/s00280-013-2175-0)

[0](#)

**AUTORES / AUTHORS:** - Tentori L; Muzi A; Dorio AS; Dolci S; Campolo F; Vernole P; Lacal PM; Praz F; Graziani G

**INSTITUCIÓN / INSTITUTION:** - Department of System Medicine, University of Rome "Tor Vergata", Via Montpellier 1, 00133, Rome, Italy.

**RESUMEN / SUMMARY:** - PURPOSE: Defective expression of the mismatch repair protein MSH3 is frequently detected in colon cancer, and down-regulation of its expression was found to decrease sensitivity to platinum compounds or poly(ADP-ribose) polymerase inhibitors (PARPi) monotherapy. We have investigated whether MSH3 transfection in MSH3-deficient colon cancer cells confers resistance to oxaliplatin or PARPi and whether their combination restores chemosensitivity. METHODS: MSH3-deficient/MLH1-proficient colon cancer HCT116MLH1 cells were transfected with the MSH3 cDNA cloned into the pcDNA3.1(-) vector. MSH3/MLH1-deficient HCT116, carrying MLH1 and MSH3 mutations on chromosome 3 and 5, respectively, and HCT116 in which

wild-type MLH1 (HCT116+3), MSH3 (HCT116+5) or both genes (HCT116+3+5) were introduced by chromosome transfer were also tested. Sensitivity to oxaliplatin and to PARPi was evaluated by analysis of clonogenic survival, cell proliferation, apoptosis and cell cycle. RESULTS: MSH3 transfection in HCT116 cells did not confer resistance to oxaliplatin or PARPi monotherapy. MSH3-proficient HCT116+5 or HCT116+3+5 cells, which were more resistant to oxaliplatin and PARPi in comparison with their MSH3-deficient counterparts, expressed higher levels of the nucleotide excision repair ERCC1 and XPF proteins, involved in the resistance to platinum compounds, and lower PARP-1 levels. In all cases, PARPi increased sensitivity to oxaliplatin. CONCLUSIONS: Restoring of MSH3 expression by cDNA transfection, rather than by chromosome transfer, did not affect colon cancer sensitivity to oxaliplatin or PARPi monotherapy; PARP-1 levels seemed to be more crucial for the outcome of PARPi monotherapy.

[607]

**TÍTULO / TITLE:** - Large-scale independent validation of the nuclear factor-kappa B p65 prognostic biomarker in prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Jul;49(10):2441-8. doi: 10.1016/j.ejca.2013.02.026. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.02.026](http://1016/j.ejca.2013.02.026)

**AUTORES / AUTHORS:** - Gannon PO; Lessard L; Stevens LM; Forest V; Begin LR; Minner S; Tennstedt P; Schlomm T; Mes-Masson AM; Saad F

**INSTITUCIÓN / INSTITUTION:** - Centre de recherche du Centre hospitalier de l'Université de Montreal (CRCHUM), Institut du cancer de Montreal, and Faculty of Medicine, Université de Montreal, Montreal, Quebec, Canada.

**RESUMEN / SUMMARY:** - PURPOSE: Over the last decade, we and others have uncovered a robust association between the nuclear localisation of nuclear factor-kappa B (NF-kappaB) p65, prostate cancer (PCa) aggressiveness and biochemical recurrence (BCR). Our goal was to validate these results in a large independent cohort of PCa patients who underwent radical prostatectomy. EXPERIMENTAL DESIGN: A set of 1826 fully annotated prostate cancers treated by radical prostatectomy were analysed in a tissue microarray (TMA) format for NF-kappaB p65 immunohistochemistry-based protein expression. We performed standard Cox proportional hazard regression models for follow-up data, bootstrap procedure for model internal validation, Harrell's concordance index for model discrimination and graphical assessment of predicted versus actual outcomes for model calibration. RESULTS: We observed a significant association between an increase in the nuclear frequency of NF-kappaB p65 and Gleason score ( $P < 0.001$ ), overall BCR ( $P < 0.001$ ) and development of metastases ( $P = 0.001$ ). NF-kappaB was found to be an independent predictor of BCR ( $P < 0.001$ , Cox regression). However its contribution to the predictive

accuracy of a multivariate model, which included preoperative PSA, Gleason score, extraprostatic extension, lymph node invasion, seminal vesicle involvement and surgical margin status, was modest. CONCLUSIONS: Our study offers validating results linking NF-kappaB p65 with disease progression using a large cohort of European men. However, the contribution of NF-kappaB to a post-surgical predictive model appears modest. Further validating work should focus on evaluating the contribution of NF-kappaB p65 in pre-treatment models.

[608]

**TÍTULO / TITLE:** - Mechanisms of action and resistance to all-trans retinoic acid (ATRA) and arsenic trioxide (AsO ) in acute promyelocytic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Hematol. 2013 May 14.

●●Enlace al texto completo (gratis o de pago) [1007/s12185-013-1354-](#)

[4](#)

**AUTORES / AUTHORS:** - Tomita A; Kiyoi H; Naoe T

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya, 466-8550, Japan, [atomita@med.nagoya-u.ac.jp](mailto:atomita@med.nagoya-u.ac.jp).

**RESUMEN / SUMMARY:** - Since the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) for the treatment of acute promyelocytic leukemia (APL), the overall survival rate has improved dramatically. However, relapse/refractory patients showing resistance to ATRA and/or As<sub>2</sub>O<sub>3</sub> are recognized as a clinically significant problem. Genetic mutations resulting in amino acid substitution in the retinoic acid receptor alpha (RARalpha) ligand binding domain (LBD) and the PML-B2 domain of PML-RARalpha, respectively, have been reported as molecular mechanisms underlying resistance to ATRA and As<sub>2</sub>O<sub>3</sub>. In the LBD mutation, ATRA binding with LBD is generally impaired, and ligand-dependent co-repressor dissociation and degradation of PML-RARalpha by the proteasome pathway, leading to cell differentiation, are inhibited. The PML-B2 mutation interferes with the direct binding of As<sub>2</sub>O<sub>3</sub> with PML-B2, and PML-RARalpha SUMOylation with As<sub>2</sub>O<sub>3</sub> followed by multimerization and degradation is impaired. To overcome ATRA resistance, utilization of As<sub>2</sub>O<sub>3</sub> provides a preferable outcome, and recently, a synthetic retinoid Am80, which has a higher binding affinity with PML-RARalpha than ATRA, has been tested in the clinical setting. However, no strategy attempted to date has been successful in overcoming As<sub>2</sub>O<sub>3</sub> resistance. Detailed genomic analyses using patient samples harvested repeatedly may help in predicting the prognosis, selecting the effective targeting drugs, and designing new sophisticated strategies for the treatment of APL.

[609]

**TÍTULO / TITLE:** - Methotrexate binds to recombinant thiopurine S-methyltransferase and inhibits enzyme activity after high-dose infusions in childhood leukaemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Clin Pharmacol. 2013 May 10.

●●Enlace al texto completo (gratis o de pago) [1007/s00228-013-1521-](#)

[9](#)

**AUTORES / AUTHORS:** - Wennerstrand P; Martensson LG; Soderhall S; Zimdahl A; Appell ML

**INSTITUCIÓN / INSTITUTION:** - Department of Physics, Chemistry and Biology, Linköping University, Linköping, Sweden.

**RESUMEN / SUMMARY:** - **PURPOSE:** Important drugs in the treatment of childhood acute lymphoblastic leukaemia (ALL) are 6-mercaptopurine (6-MP) and methotrexate (MTX). Thiopurine methyltransferase (TPMT) is a polymorphic enzyme causing variability in 6-MP response and toxicity. The aim of this study was to investigate the fluctuation in TPMT enzyme activity over time and the effect of high-dose MTX infusions on TPMT enzyme activity and 6-MP metabolites in paediatric ALL patients. **METHODS:** Fifty-three children with ALL treated according to the NOPHO-ALL 2000 protocol were included in the study. TPMT enzyme activity was measured at six different times starting from diagnosis until after the end of maintenance treatment. TPMT and 6-MP metabolites were measured before the initiation of high-dose MTX (HD-MTX) infusions and at 66 h post-infusion. The interaction between MTX and TPMT was investigated in vitro using recombinant TPMT protein and a leukaemic cell line. **RESULTS:** Forty percent of TPMT wild-type individuals had deceptively low TPMT enzyme activity according to genotype at the time of diagnosis. TPMT activity had decreased significantly 66 h after the start of HD-MTX infusions (-9.2 %;  $p = 0.013$ ). MTX bound to recombinant TPMT protein severely inhibiting TPMT enzyme activity (remaining activity 16 %). **CONCLUSIONS:** Our results show that TPMT genotyping should be performed in children with ALL, since 40 % of the children in our study who carried the wild-type TPMT gene were at risk of initial underdosing of 6-MP in cases where only TPMT enzyme activity was determined. MTX inhibits the TPMT enzyme activity after HD-MTX infusions due to protein binding.

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[610]

**TÍTULO / TITLE:** - Acceptable cardiac safety profile of neoadjuvant 5-fluorouracil, epirubicin, cyclophosphamide and celecoxib (FEC-C) for breast cancer: a subanalysis of biomarkers for cardiac injury.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biol Markers. 2013 Apr 23;28(1):e92-9. doi: 10.5301/jbm.5000012.

●●Enlace al texto completo (gratis o de pago) [5301/jbm.5000012](https://doi.org/10.5301/jbm.5000012)

**AUTORES / AUTHORS:** - Chow LW; Loo WT; Yip AY; Ng EL

**INSTITUCIÓN / INSTITUTION:** - Organisation for Oncology and Translational Research, Hong Kong - PR China and UNIMED Medical Institute, Hong Kong-PR China and Clinical Trials Centre, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong - PR China.

**RESUMEN / SUMMARY:** - Purposes: This substudy aimed to examine the changes in biomarkers for cardiac injury in patients who received neoadjuvant 5-fluorouracil, epirubicin, cyclophosphamide with concurrent celecoxib (FEC-C). Methods: Thirty-four female patients with histologically confirmed locally advanced breast cancer preoperatively received 3 cycles of FEC-C (500 mg/m<sup>2</sup>, 75 mg/m<sup>2</sup>, 500 mg/m<sup>2</sup>) with concurrent celecoxib (400 mg bid). Blood samples were drawn from patients on day (D) 0, D3, D21, D42, and D63 (end of therapy), and the serum levels of lactate dehydrogenase (LDH) and plasma levels of cardiac troponin I (cTnI) and N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) were measured with commercially available test kits. Results: All patients tolerated this regimen well. Neither life-threatening toxicity nor clinical symptoms of cardiac damage were observed. Serum LDH increased significantly from baseline after 3 cycles of FEC-C ( $p < 0.0001$ ), but the change was possibly brought about by chemotherapy-induced liver derangement. However, NT-proBNP decreased significantly ( $p = 0.009$ ), while cTnI increased nonsignificantly ( $p = 0.078$ ) after 3 cycles of FEC-C compared to baseline, although this increase was still regarded as normal. Conclusions: Short-term use of the FEC-C regimen has proven to be effective in locally advanced breast cancer, with an acceptable cardiac safety profile.

[611]

**TÍTULO / TITLE:** - The Autophagy Inhibitor Chloroquine Overcomes the Innate Resistance of Wild-Type EGFR Non-Small-Cell Lung Cancer Cells to Erlotinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Thorac Oncol. 2013 Jun;8(6):693-702. doi: 10.1097/JTO.0b013e31828c7210.

●●Enlace al texto completo (gratis o de pago)

[1097/JTO.0b013e31828c7210](https://doi.org/10.1097/JTO.0b013e31828c7210)

**AUTORES / AUTHORS:** - Zou Y; Ling YH; Sironi J; Schwartz EL; Perez-Soler R; Piperdi B

**INSTITUCIÓN / INSTITUTION:** - Departments of Medicine and Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York.

**RESUMEN / SUMMARY:** - INTRODUCTION: : The epidermal growth factor receptor (EGFR) inhibitor erlotinib is much less effective in non-small-cell lung cancer (NSCLC) tumors with wild-type EGFR, than in tumors with activating EGFR mutations. Autophagy is a tightly regulated lysosomal self-digestion

process, which may alternatively promote cell survival or type II cell death. This study assessed the role of autophagy in erlotinib-mediated cytotoxicity.

**METHODS:** : We used wild-type EGFR erlotinib-sensitive and erlotinib-resistant NSCLC cell lines to determine whether inhibiting autophagy by a therapeutic agent potentiated the antitumor activity of erlotinib in vitro and in vivo.

**RESULTS:** : Erlotinib at a clinically relevant concentration (2  $\mu$ M) induced autophagy in NSCLC cells with wild-type EGFR, and the degree of induction was greater in cells that were resistant than sensitive, suggesting that autophagy is cytoprotective. This was confirmed by knockdown of the autophagy-related gene Atg-5, and by using the autophagy inhibitor chloroquine (CQ), both of which increased the cytotoxicity of erlotinib. The synergistic activity of CQ was not because of the potentiation of erlotinib's effects on autophagy, cell-cycle arrest, and inhibition of both EGFR or downstream signaling of EGFR. Rather, CQ markedly activated apoptosis in the cells. The ability of CQ to potentiate the antitumor activity of erlotinib was also seen in mice bearing NSCLC tumor xenografts.

**CONCLUSIONS:** : The ability to adapt to anti-EGFR therapy by triggering autophagy may be a key determinant for resistance to erlotinib in wild-type EGFR NSCLC. Inhibition of autophagy by CQ represents a novel strategy to broaden the spectrum of erlotinib efficacy in wild-type EGFR NSCLC tumors.

[612]

**TÍTULO / TITLE:** - Biomarkers for predicting the response of esophageal squamous cell carcinoma to neoadjuvant chemoradiation therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Surg Today. 2013 Apr 19.

●●Enlace al texto completo (gratis o de pago) [1007/s00595-013-0580-](#)

[y](#)

**AUTORES / AUTHORS:** - Okumura H; Uchikado Y; Setoyama T; Matsumoto M; Owaki T; Ishigami S; Natsugoe S

**INSTITUCIÓN / INSTITUTION:** - Department of Digestive Surgery, Breast and Thyroid Surgery, Graduate School of Medical Sciences, Kagoshima University, Sakuragaoka 8-35-1, Kagoshima, 890-8520, Japan, [hokumura@m.kufm.kagoshima-u.ac.jp](mailto:hokumura@m.kufm.kagoshima-u.ac.jp).

**RESUMEN / SUMMARY:** - This review summarizes and evaluates the literature regarding the biomarkers for predicting the response and/or prognosis of esophageal squamous cell carcinoma (ESCC) patients treated with neoadjuvant chemoradiation therapy (CRT). There are seven categories of molecules known to correlate with the response and/or prognosis: tumor suppressors (p53, p21), cell cycle regulators (Cyclin D1, CDC25B, 14-3-3sigma), DNA repair molecules (p53R2, ERCC1), drug resistance proteins [metallothionein (MT)], angiogenic factors (VEGF), molecules involved in cell proliferation/invasion/metastasis (Ki-67, COX-2) and hedgehog signaling

molecules (Gli-1). Of the above molecules, the tumor suppressor p53 is expected to be a representative biomarker for predicting the response and prognosis. The cell cycle markers CDC25B and 14-3-3sigma have potential as response biomarkers independent of the p53 status. The DNA repair markers, p53R2 or ERCC1, angiogenic molecule (VEGF), and hedgehog signaling pathway factor Gli-1 also have potential to predict the response and prognosis of ESCC. However, there are still many unanswered questions with regard to predicting the clinical effects of neoadjuvant CRT.

[613]

**TÍTULO / TITLE:** - Predictors of biomarkers guiding targeted therapeutic strategies in locally advanced lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer J. 2013 May-Jun;19(3):263-71. doi: 10.1097/PPO.0b013e318297216a.

●●Enlace al texto completo (gratis o de pago)

[1097/PPO.0b013e318297216a](#)

**AUTORES / AUTHORS:** - Cottini F; Lautenschlaeger T

**INSTITUCIÓN / INSTITUTION:** - From the \*Dana Farber Cancer Institute, Boston, MA; and daggerDepartment of Radiation/Oncology, Ohio State University, Columbus, OH.

**RESUMEN / SUMMARY:** - Lung cancer accounts for the majority of cancer-related deaths worldwide. We sought out to summarize the current state of molecular predictors for response and toxicity in locally advanced lung cancer. Several changes have been introduced in recent years in the standard-of-care treatment of advanced non-small cell lung cancer based on the identification of specific molecular alterations that determine response probability to certain therapies. Eligibility for these treatments is assessed by a biomarker test, evaluating if the molecular alteration is present or not in a patient's tumor. In particular, tissue testing for epidermal growth factor receptor and anaplastic lymphoma kinase alterations is currently recommended for certain patients with advanced non-small cell lung cancer, whereas excision repair cross-complementation group 1 and ribonucleotide reductase 1 as markers for outcome after platinum and gemcitabine therapy are promising but are currently not recommended outside a clinical trial. However, their application to the therapy of locally advanced disease is still mostly investigational. Moreover, additional candidate markers for response and toxicity for locally advanced lung cancer are under further investigation.

[614]

**TÍTULO / TITLE:** - Predicting the functional consequences of cancer-associated amino acid substitutions.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioinformatics. 2013 May 17.

●●Enlace al texto completo (gratis o de pago)

[1093/bioinformatics/btt182](#)

**AUTORES / AUTHORS:** - Shihab HA; Gough J; Cooper DN; Day IN; Gaunt TR

**INSTITUCIÓN / INSTITUTION:** - Bristol Centre for Systems Biomedicine and MRC CAiTE Centre, School of Social and Community Medicine, University of Bristol, Bristol BS8 2BN, Department of Computer Science, University of Bristol, The Merchant Venturers Building, Bristol BS8 1UB and Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK.

**RESUMEN / SUMMARY:** - MOTIVATION: The number of missense mutations being identified in cancer genomes has greatly increased as a consequence of technological advances and the reduced cost of whole-genome/whole-exome sequencing methods. However, a high proportion of the amino acid substitutions detected in cancer genomes have little or no effect on tumour progression (passenger mutations). Therefore, accurate automated methods capable of discriminating between driver (cancer-promoting) and passenger mutations are becoming increasingly important. In our previous work, we developed the Functional Analysis through Hidden Markov Models (FATHMM) software and, using a model weighted for inherited disease mutations, observed improved performances over alternative computational prediction algorithms. Here, we describe an adaptation of our original algorithm that incorporates a cancer-specific model to potentiate the functional analysis of driver mutations. RESULTS: The performance of our algorithm was evaluated using two separate benchmarks. In our analysis, we observed improved performances when distinguishing between driver mutations and other germ line variants (both disease-causing and putatively neutral mutations). In addition, when discriminating between somatic driver and passenger mutations, we observed performances comparable with the leading computational prediction algorithms: SPF-Cancer and TransFIC. Availability and implementation: A web-based implementation of our cancer-specific model, including a downloadable stand-alone package, is available at <http://fathmm.biocompute.org.uk>. CONTACT: [fathmm@biocompute.org.uk](mailto:fathmm@biocompute.org.uk) SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

[615]

**TÍTULO / TITLE:** - Expression and prognostic significance of the oncogenic K2P potassium channel KCNK9 (TASK-3) in ovarian carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1401-8.

**AUTORES / AUTHORS:** - Innamaa A; Jackson L; Asher V; Van Shalkwyk G; Warren A; Hay D; Bali A; Sowter H; Khan R

**INSTITUCIÓN / INSTITUTION:** - School of Graduate Entry Medicine and Health, University of Nottingham, Upton Road, Derby, UK.

**RESUMEN / SUMMARY:** - BACKGROUND/AIMS: The TWIK-related acid sensitive K(+) channel-3 (TASK-3) is an oncogenic potassium channel. We investigated the expression of TASK-3 in human ovaries, examined its prognostic significance, and determined effects of TASK-3 blockers on cell proliferation and apoptosis. MATERIALS AND METHODS: Immunofluorescence and western blotting were used to investigate TASK-3 expression in two ovarian cancer cell lines, normal ovarian surface epithelium and cancer. Immunohistochemistry quantified expression in an ovarian cancer tissue microarray. The effect of TASK-3 blocking agents on cell proliferation was investigated with the CellTiter 96® Aqueous Non-Radioactive Cell Proliferation assay and on apoptosis with flow cytometry. RESULTS: TASK-3 expression was confirmed by immunofluorescence in the SKOV-3 and OVCAR-3 cell lines, normal ovaries (n=4) and ovarian tumours (n=4) and by western blotting in normal ovaries (n=6) and ovarian tumours (n=22). Immunohistochemistry demonstrated immunostaining in 99% of tumours (n=230). Increased immunostaining conferred a survival advantage (p=0.002; median survival of >24 months). TASK-3 blockers caused a significant reduction in cell proliferation and an increase in apoptosis in the SKOV-3 and OVCAR-3 cell lines. CONCLUSION: TASK-3 is expressed in epithelial ovarian cancer, conferring a significant survival advantage on patients with increased expression. TASK-3-modulating agents have a significant effect on cell proliferation and apoptosis. Based on these results, we propose that TASK-3 could prove to be both a novel tumour marker and a new therapeutic target in ovarian cancer, but further investigation is required.

[616]

**TÍTULO / TITLE:** - Implications of the histological determination of microRNAs in the screening, diagnosis and prognosis of colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Surg Oncol. 2013 Apr 22. doi: 10.1002/jso.23344.

●●Enlace al texto completo (gratis o de pago) [1002/jso.23344](#)

**AUTORES / AUTHORS:** - Menendez P; Villarejo P; Padilla D; Menendez JM; Rodriguez-Montes JA

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Gutierrez Ortega Hospital, Ciudad Real, España.

**RESUMEN / SUMMARY:** - MicroRNAs are short non-coding RNA molecules that participate in the regulation of gene expression. Several studies have demonstrated the involvement of microRNAs in oncogenesis and a variety of physiological functions. We conducted a literature review of studies that evaluated histological microRNAs in colorectal cancer. Although additional clinical studies are required to substantiate the relationship between microRNAs

and colorectal cancer, there is preliminary evidence that microRNAs are related to the diagnosis and prognosis of colorectal cancer. J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

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[617]

**TÍTULO / TITLE:** - Antitumor effects of a novel histone deacetylase inhibitor NK-HDAC-1 on breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):499-505. doi: 10.3892/or.2013.2434. Epub 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2434](#)

**AUTORES / AUTHORS:** - Li ZH; Zhang XB; Han XQ; Feng CR; Wang FS; Wang PG; Shen J; Shi YK

**INSTITUCIÓN / INSTITUTION:** - National Glycoengineering Research Center and School of Pharmaceutical Sciences, Shandong University, Jinan, Shandong 250012, P.R. China.

**RESUMEN / SUMMARY:** - Histone deacetylases (HDACs) are overexpressed in various types of primary human cancer and have become attractive targets for cancer therapy. We designed and synthesized a series of new class of HDAC inhibitors (HDACi). Among these, S-(E)-3-(1-(1-(benzo[d]oxazol-2-yl)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)-N-hydr oxyacrylamide (NK-HDAC-1) showed potent antitumor activity. In the present study, we examined the antitumor effects of NK-HDAC-1 on breast cancer in vitro and in vivo. The inhibitory effects of NK-HDAC-1 on HDAC enzyme activity and cell growth were more potent compared to suberoylanilide hydroxamic acid (SAHA). NK-HDAC-1 caused G1 cell cycle arrest at concentrations below 0.2 microM and G2/M arrest at concentrations above 0.4 microM through p21 upregulation and cyclin D1 downregulation. NK-HDAC-1 induced hyperacetylation of histone H3 and H4 around the promoter region of p21. NK-HDAC-1 promoted apoptosis in MDA-MB231 breast cancer cells by activating both the intrinsic and the extrinsic pathway NK-HDAC-1 at doses of 3, 10 and 30 mg/kg reduced the tumor volume in MDA-MB231 xenografts by 25.9, 48.8 and 63.6%, respectively. The results suggested that NK-HDAC-1 may be a promising therapeutic candidate in treating human breast cancer.

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[618]

**TÍTULO / TITLE:** - Prostate-specific antigen (PSA) rate of decline post external beam radiotherapy predicts prostate cancer death.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Radiother Oncol. 2013 Apr 23. pii: S0167-8140(13)00161-8. doi: 10.1016/j.radonc.2013.03.030.

●●Enlace al texto completo (gratis o de pago)

[1016/j.radonc.2013.03.030](#)

**AUTORES / AUTHORS:** - Shi Z; Pinnock CB; Kinsey-Trotman S; Borg M; Moretti KL; Walsh S; Kopsaftis T

**INSTITUCIÓN / INSTITUTION:** - Discipline of Medicine, University of Adelaide, SA, Australia. Electronic address: [zumin.shi@adelaide.edu.au](mailto:zumin.shi@adelaide.edu.au).

**RESUMEN / SUMMARY:** - BACKGROUND AND PURPOSE: To assess the association between PSA velocity (PSAV) in the first 24 months after external beam radiotherapy (EBRT) and prostate cancer-specific mortality (PCSM) and all cause mortality. MATERIALS AND METHODS: All eligible patients in the South Australian (SA) Prostate Cancer Clinical Outcomes registry were followed. 848 Patients treated by definitive EBRT with more than one PSA recorded in the two year post-treatment were included. We calculated PSAV by linear regression. RESULTS: The mean number of PSA measurements in the 2 year period was 4.4 (SD1.9). The median PSAVs across quartiles (Q1-Q4) were -4.17, -1.29, -0.38 and 0.20ng/ml/yr. In multivariable analysis, a U-shaped relationship was seen between PSAV and PCSM with Q1-Q4 hazard ratios (HR) being 3.82 (1.46-10.00), 3.07 (1.10-8.58), 1, 5.15 (1.99-13.30) respectively. HR for all cause mortality in a similar model were 1.79 (1.07-2.98), 1.55 (0.93-2.59), 1.00 and 1.74 (1.04-2.90) for Q1 to Q4 respectively. A rapid PSA decline in the first year was a strong predictor of PCSM. However, in the second year PSA increase was positively associated with PCSM. CONCLUSION: A rapid decline in PSA in the first year following EBRT is positively associated with PCSM. This may be a useful early indicator of the need for additional therapies.

[619]

**TÍTULO / TITLE:** - Efficacy, safety, pharmacokinetics and biomarker findings in patients with HER2-positive advanced or metastatic breast cancer treated with lapatinib in combination with capecitabine: results from 51 Japanese patients treated in a clinical study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s12282-013-0475-](#)

[1](#)

**AUTORES / AUTHORS:** - Iwata H; Fujii H; Masuda N; Mukai H; Nishimura Y; Katsura K; Ellis CE; Gagnon RC; Nakamura S

**INSTITUCIÓN / INSTITUTION:** - Aichi Cancer Center Hospital, Breast Oncology, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi, 464-8681, Japan, [hiwata@aichi-cc.jp](mailto:hiwata@aichi-cc.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The results from a phase III trial conducted outside of Japan demonstrated a significant improvement in time to progression (TTP) when lapatinib was combined with capecitabine compared with capecitabine alone in patients with HER2-positive advanced or metastatic

breast cancer. In this clinical study of lapatinib in combination with capecitabine, efficacy, safety, pharmacokinetics (PK) and biomarkers were investigated in Japanese patients with HER2-positive advanced or metastatic breast cancer treated with prior trastuzumab. METHODS: Eligible women received lapatinib 1250 mg once daily and capecitabine 1000 mg/m<sup>2</sup> twice daily on days 1 through 14 of a 21-day cycle. The primary endpoint was the clinical benefit rate (CBR: complete response, partial response or stable disease for at least 24 weeks). RESULTS: Lapatinib in combination with capecitabine was well tolerated in the 51 patients enrolled in this study. CBR was 59 % (95 % CI 44.2, 72.4), and the median TTP in the Kaplan-Meier estimate was 36 weeks (95 % CI 27.1, 48.0). The majority of drug-related adverse events were mild to moderate (grade 1 or 2); the most common adverse events reported were palmar-plantar erythrodysesthesia syndrome (76 %), diarrhea (67 %) and stomatitis (41 %). CONCLUSIONS: Lapatinib in combination with capecitabine in Japanese HER2-positive breast cancer patients was well tolerated. Overall, our findings on the efficacy, safety and PK were similar to those reported from the overseas studies.

[620]

**TÍTULO / TITLE:** - Pulmonary adenocarcinomas with micropapillary component significantly correlate with recurrence, but can be well controlled with EGFR tyrosine kinase inhibitors in the early stages.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Apr 27. pii: S0169-5002(13)00150-5. doi: 10.1016/j.lungcan.2013.04.003.

●●Enlace al texto completo (gratis o de pago)

[1016/j.lungcan.2013.04.003](#)

**AUTORES / AUTHORS:** - Sumiyoshi S; Yoshizawa A; Sonobe M; Kobayashi M; Fujimoto M; Tsuruyama T; Date H; Haga H

**INSTITUCIÓN / INSTITUTION:** - Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan.

**RESUMEN / SUMMARY:** - Pulmonary adenocarcinoma with a micropapillary component (PA-MPC) is known to exhibit biologically aggressive behavior. The aim of this study was to evaluate the clinicopathological characteristics of early-stage PA-MPC and to investigate the correlation between PA-MPC and epidermal growth factor receptor (EGFR) or KRAS mutation status. We reviewed 440 PA patients who underwent resection. We defined PA-MPC as adenocarcinoma with MPC occupying at least 5% of the entire tumor. EGFR and KRAS mutations were detected using established methods. Of the 440 cases, 256 cases were classified as stage IA, of which 53 cases (20.7%) had MPC. The 5-year disease-free survival rates in the MPC-negative and MPC-positive groups of patients with stage IA tumors were 92.1% and 77.6%, respectively. The difference in these rates was statistically significant ( $p=0.003$ ),

whereas the difference in overall survival between the groups was not statistically significant ( $p=0.973$ ). The mean percentage of MPC was 20.4% in the recurrent group and 18.3% in the non-recurrent group, with no significant correlation ( $p=0.996$ ). Of the 10 recurrent cases, 6 cases exhibited EGFR mutations; the 5 cases treated with a tyrosine kinase inhibitor (TKI) achieved long survival (median, 64.6 months). No KRAS mutations were detected in any of the 10 cases. PA-MPCs were strongly associated with recurrence, but were not influenced by the MPC percentage even in early-stage lesions. Moreover, PA-MPCs with recurrence were associated with relatively better survival. These findings indicate that PA-MPCs were biologically aggressive but could be controlled with EGFR-TKIs.

[621]

**TÍTULO / TITLE:** - Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Dermatolog Treat. 2013 May 21.

●●Enlace al texto completo (gratis o de pago)

[3109/09546634.2013.800184](#)

**AUTORES / AUTHORS:** - Di Lernia V; Ricci C; Lallas A; Ficarelli E

**INSTITUCIÓN / INSTITUTION:** - Unit of Dermatology, Arcispedale Santa Maria Nuova IRCCS , Reggio Emilia , Italy.

**RESUMEN / SUMMARY:** - Background: Anti-tumor necrosis factor (TNF)-alpha therapies represent a significant innovation in therapy for psoriasis. However, a significant number of psoriasis patients do not respond well to TNF blockers or show an insufficient control of disease activity on a long-term basis.

Objective/aim: The aim of this study was to recognize specific clinical factors that could be associated with a non-response to any available TNF blockers in patients with moderate-to-severe plaque psoriasis. Materials and methods: The authors reviewed the medical records of all patients who had started etanercept, infliximab, adalimumab and had achieved a minimum of 24 months follow-up. The authors identified subjects who were not responsive to all available anti-TNF agents, whatever the chronology of their use. Results: A total of 110 patients were retrospectively examined. Thirteen patients were identified as “non-responders” to all available TNF-alpha blockers. Current smoking at the start of anti-TNF therapy was associated with non-response to TNF blockers. The group of “non-responders” presented a high mean body mass index and a high baseline PASI score with respect to the group of responders. Conclusions: The data showed that the majority of non-responder patients were smokers, overweight or obese and had a high baseline PASI score. Concomitant arthritis was not significantly associated with non-response.

[622]

**TÍTULO / TITLE:** - Interleukin-4 receptor alpha-based hybrid peptide effectively induces antitumor activity in head and neck squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jun;29(6):2147-53. doi: 10.3892/or.2013.2387. Epub 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2387](#)

**AUTORES / AUTHORS:** - Seto K; Shoda J; Horibe T; Warabi E; Ishige K; Yamagata K; Kohno M; Yanagawa T; Bukawa H; Kawakami K

**INSTITUCIÓN / INSTITUTION:** - Department of Oral and Maxillofacial Surgery, Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki 305-8575, Japan.

**RESUMEN / SUMMARY:** - Interleukin-4 receptor alpha (IL-4Ralpha) is highly expressed on the surface of various human solid tumors including head and neck squamous cell carcinoma (HNSCC). We designed a novel IL-4Ralpha-lytic hybrid peptide composed of a binding peptide to IL-4Ralpha and a cell-lytic peptide. In the present study, we evaluated the antitumor activity of the IL-4Ralpha-lytic hybrid peptide as a novel molecular-targeted therapy in HNSCC. Immunoblot analysis revealed that IL-4Ralpha was expressed in all tested HNSCC cell lines (HSC-2, HSC-3, HSC-4, Ca9-22 and OSC-19), but not in a human normal keratinocyte (HaCaT) cell line. Immunohistochemical expression levels of IL-4Ralpha in HNSCC tissues were higher compared to those in normal epithelial tissue. The IL-4Ralpha-lytic hybrid peptide showed cytotoxic activity in all five cancer cell lines with a concentration that killed 50% of all cells (IC50) as low as 10 microM. HaCaT cells were less sensitive to this peptide with an IC50 of >30 microM. In addition, intratumoral administration of IL-4Ralpha-lytic hybrid peptide significantly inhibited tumor growth in a xenograft model of human HNSCC in vivo. These results indicate that the IL-4Ralpha-lytic hybrid peptide may serve as a potent agent to provide a novel therapy for patients with HNSCC.

[623]

**TÍTULO / TITLE:** - Prognostic value of HOXB7 mRNA expression in human oesophageal squamous cell cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomarkers. 2013 Jun;18(4):297-303. doi: 10.3109/1354750X.2013.773380. Epub 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago)

[3109/1354750X.2013.773380](#)

**AUTORES / AUTHORS:** - Xie X; Zhang SS; Wen J; Yang H; Luo KJ; Yang F; Hu Y; Fu JH

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center , Guangzhou , People's Republic of China .

**RESUMEN / SUMMARY:** - Abstract Objective: This study was to determine the role of HOXB7 in predicting outcomes of patients with oesophageal squamous cell cancer (OSCC). Methods: Samples were collected from 179 OSCC patients. HOXB7 mRNA expression was measured by quantitative real-time polymerase chain reaction. Results: HOXB7 mRNA expression was up-regulated in 85.1% of OSCC tumorous tissues, and correlated with age, pathological T and N category, as well as cancer-specific survival (CSS). However, subgroup analysis revealed its discernibility on CSS was only pronounced in early stage. Conclusions: HOXB7 mRNA expression might serve as a novel prognostic biomarker for resected OSCC patients in early stage.

[624]

**TÍTULO / TITLE:** - Sprengerinin C exerts anti-tumorigenic effects in hepatocellular carcinoma via inhibition of proliferation and angiogenesis and induction of apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 May 15. pii: S0014-2999(13)00331-2. doi: 10.1016/j.ejphar.2013.04.026.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ejphar.2013.04.026](#)

**AUTORES / AUTHORS:** - Zeng KW; Li N; Dong X; Ma ZZ; Jiang Y; Jin HW; Tu PF

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, PR China.

**RESUMEN / SUMMARY:** - The multi-targeted therapy for liver cancer has been considered as a novel strategy to fight hepatocellular carcinoma. In this study, we first found that sprengerinin C, a naturally derived compound strongly suppressed tumor angiogenesis in human umbilical vein endothelial cells. A mechanism study revealed that sprengerinin C blocked vascular endothelial growth factor receptor 2-dependent phosphoinositide 3-kinase/Akt/mTOR/matrix metalloproteinase and p38 MAPK/matrix metalloproteinase pathways, two major pathways for tumor angiogenesis. Moreover, sprengerinin C inhibited vascular endothelial growth factor release, a vital event for early angiogenesis response, from hypoxic HepG-2/BEL7402 cells by suppressing hypoxia-inducible factor-1alpha transcriptional activity. Furthermore, sprengerinin C induced HepG-2/BEL7402 cell apoptosis by activating NADPH oxidase/reactive oxygen species-dependent caspase apoptosis pathway and suppressed HepG-2/BEL7402 cell growth through p53-mediated G2/M-phase arrest. Sprengerinin C also showed a significant anti-tumor effect in the nude mouse xenograft model of human hepatocellular carcinoma. These results provide new insights into development of potent

candidate compounds for liver cancer through affecting multiple tumor progression steps of angiogenesis, apoptosis and proliferation.

[625]

**TÍTULO / TITLE:** - Association of interleukin 18, interleukin 2, and tumor necrosis factor polymorphisms with subacute sclerosing panencephalitis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - DNA Cell Biol. 2013 Jun;32(6):336-40. doi: 10.1089/dna.2013.1997. Epub 2013 May 8.

●●Enlace al texto completo (gratis o de pago) [1089/dna.2013.1997](http://1089/dna.2013.1997)

**AUTORES / AUTHORS:** - Piskin IE; Karakas-Celik S; Calik M; Abuhandan M; Kolsal E; Genc GC; Iscan A

**INSTITUCIÓN / INSTITUTION:** - 1 Department of Pediatrics, Bulent Ecevit University Faculty of Medicine , Zonguldak, Turkey .

**RESUMEN / SUMMARY:** - Subacute sclerosing panencephalitis (SSPE) is a progressive inflammatory and degenerative disorder of the central nervous system. The measles virus (MV) and host and environmental factors are involved in the development of SSPE, but the precise mechanism by which the MV causes SSPE is still unknown. Studies have indicated that in SSPE patients, specific polymorphisms of certain genes are most likely involved in impairing the host's ability to eradicate the MV. The purpose of our study was to elucidate the role of polymorphisms in the genes encoding interleukin (IL)-2, IL-18, and tumor necrosis factor alpha (TNF-alpha) in the development of SSPE. Using the polymerase chain reaction with sequence-specific primers, the single-nucleotide polymorphisms (SNPs) of the promoter regions of IL-2 (-330), TNF-alpha (-308), and IL-18 (-137 and -607) were studied in 54 patients with SSPE and 72 healthy controls. The frequency of SSPE patients with the AA genotype of IL-18 at position -607 was significantly higher than the frequency of those with the CC genotype ( $p < 0.001$ , odds ratio [OR]: 5.76), and a significantly higher proportion of patients had the C allele at -137 compared with the controls ( $p = 0.002$ , OR: 2.72). In a haplotype analysis of two SNPs in the IL-18 gene, the frequency of the CA haplotype was significantly higher in SSPE patients ( $p < 0.001$ , OR: 3.99) than in the controls. The IL-2 (-330) and TNF-alpha (-308) polymorphisms revealed no significant differences. In conclusion, these data suggest that the IL-18 gene polymorphisms at position -607 and -137 might be genetic risk factors for the SSPE disease.

[626]

**TÍTULO / TITLE:** - Prognostic value of cyclin D1 expression in tumor-free surgical margins in head and neck squamous cell carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Otolaryngol. 2013 May 22.

●●Enlace al texto completo (gratis o de pago)

[3109/00016489.2013.795287](https://doi.org/10.1016/j.marpolbul.2013.03.041)

**AUTORES / AUTHORS:** - Sakashita T; Homma A; Suzuki S; Hatakeyama H; Kano S; Mizumachi T; Oridate N; Fukuda S

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology- Head and Neck Surgery, Hokkaido University Graduate School of Medicine , Sapporo.

**RESUMEN / SUMMARY:** - Abstract Conclusion: It was proved that cyclin D1-positive status in surgical margins was an independent prognostic indicator of local recurrence. The expression of cyclin D1 in tumor-free surgical margins may better predict local recurrence in patients with head and neck squamous cell carcinoma (HNSCC) after surgical treatment with curative intent. Objective: This retrospective study aimed to determine the prognostic indicators for local recurrence in HNSCC. Methods: A total of 116 HNSCC patients who underwent surgical treatment with curative intent and had histopathologically tumor-free margins were eligible for this study. The expression of p53 and cyclin D1 was assessed by immunohistochemical staining in surgical margins as well as in tumor specimens. Results: In all, 63 patients (54.3%) had p53-positive tumor specimens and 34 patients (29.3%) had p53-positive margins. Seventy-six patients (65.6%) had cyclin D1-positive tumor specimens and 54 patients (46.6%) had cyclin D1-positive margins. A significant difference in local control rates was observed between patients with cyclin D1-positive and -negative margins (77.2% vs 91.5%, log rank test,  $p = 0.0139$ ). Multivariate Cox proportional hazards testing indicated that the hazard ratio of cyclin D1-positive margins for local recurrence was 4.58 (95% confidence interval 1.14-21.69,  $p = 0.0304$ ).

[627]

**TÍTULO / TITLE:** - Increased liver apoptosis and tumor necrosis factor expression in Atlantic bluefin tuna (*Thunnus thynnus*) reared in the northern Adriatic Sea.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mar Pollut Bull. 2013 Apr 27. pii: S0025-326X(13)00183-5. doi: 10.1016/j.marpolbul.2013.03.041.

●●Enlace al texto completo (gratis o de pago)

[1016/j.marpolbul.2013.03.041](https://doi.org/10.1016/j.marpolbul.2013.03.041)

**AUTORES / AUTHORS:** - Corriero A; Zupa R; Pousis C; Santamaria N; Bello G; Jirillo E; Carrassi M; De Giorgi C; Passantino L

**INSTITUCIÓN / INSTITUTION:** - Department of Emergency and Organ Transplant (D.E.T.O.), Section of Veterinary Clinics and Animal Production, University of Bari Aldo Moro, 70010 Valenzano, Bari, Italy.

**RESUMEN / SUMMARY:** - The Atlantic bluefin tuna *Thunnus thynnus* (ABFT) is intensely fished in the Mediterranean Sea to supply a prosperous capture-based mariculture industry. Liver apoptotic structures and tumor necrosis factor (TNF) gene expression were determined in: wild ABFT caught in the eastern

Atlantic; juvenile ABFT reared in the central Adriatic Sea; juvenile ABFT reared in the northern Adriatic Sea; adult ABFT reared in the western Mediterranean. The highest density of liver apoptotic structures was found in the juveniles from the northern Adriatic. Two partial TNF cDNAs (TNF1 and TNF2) were cloned and sequenced. TNF1 gene expression was higher in juveniles than in adults. The highest expression of TNF2 was found in the juveniles from the northern Adriatic. These findings might be related to the juvenile exposure to environmental pollutants.

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[628]

**TÍTULO / TITLE:** - Decreased expression of the mitochondrial metabolic enzyme aconitase (ACO2) is associated with poor prognosis in gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):552. Epub 2013 Apr 2.

**AUTORES / AUTHORS:** - Wang P; Mai C; Wei YL; Zhao JJ; Hu YM; Zeng ZL; Yang J; Lu WH; Xu RH; Huang P

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in Southern China, Sun Yat-sen University Cancer Center, Guangzhou 510060, China.

**RESUMEN / SUMMARY:** - Alterations in energy metabolism play a major role in cancer development. Aconitase (ACO2) is an essential enzyme located in the mitochondria and catalyzes the interconversion of citrate and isocitrate in the tricarboxylic acid cycle. Recent studies suggest that the expression of ACO2 may be altered in certain types of cancer. The purpose of this study was to examine ACO2 expression in clinical tumor specimens from patients with gastric cancer and to evaluate the clinical relevance of ACO2 expression in gastric cancer. A total of 456 paraffin-embedded gastric cancer tissues and 30 pairs of freshly frozen tissues were used in this study. Real-time quantitative reverse transcription polymerase chain reaction, western blotting, and immunohistochemical staining were performed to measure ACO2 expression in tumor tissues and matched adjacent non-tumorous tissues. The results showed that the expression of ACO2 was significantly down-regulated in gastric cancer tissues compared with matched adjacent nontumorous tissues and was associated with clinical stage ( $p = 0.001$ ), T classification ( $p = 0.027$ ), N classification ( $p = 0.012$ ), M classification ( $p = 0.002$ ), and pathological differentiation states ( $p = 0.036$ ). Patients with lower ACO2 expression had a shorter survival time than those with higher ACO2 expression. Univariate and multivariate analyses indicated that ACO2 expression functions as an independent prognostic factor ( $p < 0.001$ ). Our data suggested that ACO2 could play an important role in gastric cancer and may potentially serve as a prognostic biomarker.

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[629]

**TÍTULO / TITLE:** - TAM receptors in apoptotic cell clearance, autoimmunity, and cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Autoimmunity. 2013 May 10.

●●Enlace al texto completo (gratis o de pago)

[3109/08916934.2013.794515](#)

**AUTORES / AUTHORS:** - Nguyen KQ; Tsou WI; Kottenko S; Birge RB

**RESUMEN / SUMMARY:** - Receptor tyrosine kinases, Tyro-3, Axl and Mer, collectively designated as TAM, are involved in the clearance of apoptotic cells. TAM ligands, Gas6 and Protein S, bind to the surfaces of apoptotic cells, and at the same time, interact directly with TAM expressed on phagocytes, impacting the engulfment and clearance of apoptotic cells and debris. The well-tuned and balanced actions of TAM may affect a variety of human pathologies including autoimmunity, retinal degeneration, and cancer. This article emphasizes some of the emerging findings and mechanistic insights into TAM functions that are clinically relevant and possibly therapeutically targeted.

[630]

**TÍTULO / TITLE:** - Cytokeratin 19 Fragment Predicts the Efficacy of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor in Non-Small-Cell Lung Cancer Harboring EGFR Mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Thorac Oncol. 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago)

[1097/JTO.0b013e31828c3929](#)

**AUTORES / AUTHORS:** - Tanaka K; Hata A; Kaji R; Fujita S; Otsoshi T; Fujimoto D; Kawamura T; Tamai K; Takeshita J; Matsumoto T; Monden K; Nagata K; Otsuka K; Nakagawa A; Tachikawa R; Otsuka K; Tomii K; Katakami N

**INSTITUCIÓN / INSTITUTION:** - \*Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Minatojima-Minamimachi, Chuo-Ku, Kobe, Japan; and daggerDepartment of Respiratory Medicine, Kobe City Medical Center, General Hospital, Minatojima-Minamimachi, Chuo-Ku, Kobe, Hyogo, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND:: EGFR gene mutation is independently associated with a favorable response in non-small-cell lung cancer (NSCLC) patients receiving epidermal growth factor receptor -tyrosine kinase inhibitors (EGFR-TKIs), regardless of sex or smoking history. Squamous cell carcinoma patients harboring EGFR mutations show a significantly worse response to EGFR-TKIs compared with adenocarcinoma patients. We hypothesized that the serum cytokeratin 19 fragment (CYFRA 21-1) is associated with the efficacy of EGFR-TKIs in EGFR-mutated NSCLC patients. METHODS:: We retrospectively screened 160 NSCLC patients harboring EGFR mutations, who had received either gefitinib, or erlotinib between 1992 and

2011. Patients were screened for clinical characteristics, the efficacy of EGFR-TKI, and tumor markers (carcinoembryonic antigen [CEA]/CYFRA 21-1) at the initial diagnosis. RESULTS:: Of 160 eligible patients treated with EGFR-TKIs, 77 patients with high CYFRA 21-1 level (>2 ng/ml) showed significantly shorter progression-free survival (PFS) than the 83 patients with normal CYFRA 21-1 level (median PFS, 7.5 versus 13.3 months;  $p < 0.001$ ). No significant difference in PFS was observed between the high-CEA group (>5 ng/ml) and the normal-CEA group (median PFS, 8.6 versus 11.2 months;  $p = 0.242$ ). A multivariate analysis revealed that high CYFRA 21-1 level is independently associated with PFS (hazard ratio, 1.27;  $p = 0.002$ ). No significant difference in overall survival was observed between the high- and the normal-CYFRA 21-1 groups (median overall survival, 24.8 versus 39.1 months;  $p = 0.104$ ). CONCLUSIONS:: Patients with a high CYFRA 21-1 level have significantly shorter PFS. CYFRA 21-1 is not a prognostic but a predictive marker of EGFR-TKI treatment in EGFR-mutated NSCLC patients.

[631]

**TÍTULO / TITLE:** - Biomarkers of sensitivity to potent and selective antitumor 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F203) in ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 May 20. doi: 10.1002/jcb.24589.

●●Enlace al texto completo (gratis o de pago) [1002/jcb.24589](#)

**AUTORES / AUTHORS:** - Callero MA; Luzzani GA; de Dios DO; Bradshaw TD; Perez AI

**INSTITUCIÓN / INSTITUTION:** - National Scientific Council (CONICET), Argentina; Research Area, Institute of Oncology "Angel H. Roffo", University of Buenos Aires, Avenue San Martin 5481, C1417DTB, Ciudad de Buenos Aires, Argentina.

**RESUMEN / SUMMARY:** - 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F203, NSC 703786) lysylamide belongs to a novel mechanistic class of antitumor agents. It elicits activity against ovarian, breast, kidney and colorectal cancer models. In sensitive breast cancer cells, 5F203 activates aryl hydrocarbon receptor (AhR) signaling. Herein, we evaluate the role of AhR in 5F203 activity in two ovarian cancer cell lines: IGROV-1 (sensitive to 5F203), SKOV-3 (resistant to this agent). In addition, cancer cells have been isolated from ascites fluid of ovarian cancer patients; sensitivity to 5F203 and concurrent AhR signal transduction has been examined in ascites-isolated ovarian cancer patients' cells. 5F203 induced enhanced CYP1A1 expression, AhR translocation and ROS formation in IGROV-1 cells and ascites-isolated ovarian cancer cells that were sensitive to 5F203. In IGROV-1 cells 5F203-induced ROS formation was accompanied by JNK, ERK and P38MAPK phosphorylation, DNA damage and cell cycle arrest prior to apoptosis. In contrast, 5F203 failed to induce CYP1A1 expression, AhR translocation or

oxidative stress in 5F203-resistant SKOV-3 cells, or in ovarian cancer ascites cells inherently resistant to this agent. We propose that AhR may represent a new molecular target in the treatment of ovarian tumors and 5F203 may exemplify a potential novel treatment. Furthermore, putative biomarkers of sensitivity to this agent have been identified. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[632]

**TÍTULO / TITLE:** - Galectin-7 levels predict radiation response in squamous cell carcinoma of the cervix.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Apr 30. pii: S0090-8258(13)00312-0. doi: 10.1016/j.ygyno.2013.04.056.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.04.056](#)

**AUTORES / AUTHORS:** - Tsai CJ; Sulman EP; Eifel PJ; Jhingran A; Allen PK; Deavers MT; Klopp AH

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** We previously found that galectin-7 was upregulated in patients with cervical cancer who remained recurrence-free after chemoradiation. We hypothesized that pretreatment levels of galectin-7 predict radiation response in patients with squamous cell carcinoma (SCC) of the cervix. **METHODS:** Galectin-7 expression was assessed by immunohistochemical staining of a tissue microarray of paraffin-embedded specimens from 161 patients with cervical SCC treated with definitive radiation therapy in 1980-1999. Galectin-7 expression was scored as absent or present. Distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) were computed using the Kaplan-Meier method and log-rank tests. **RESULTS:** The median age at diagnosis was 45 years (range 21-85) and median follow-up interval was 71 months (range 0-285). Of the 161 patients, 105 (65%) had FIGO stage IB disease, 18 (11%) stage IIA, and 38 (24%) stage IIB. Median tumor diameter was 5.5 cm (range 3.5-8). Seven patients (4%) received concurrent chemotherapy; 139 patients (86%) had galectin-7-positive tumors and 22 (14%) galectin-7-negative tumors. Five-year DMFS rates for patients with galectin-7-positive versus -negative tumors were 73% and 55% ( $p=0.05$ ); DSS, 65% and 36% ( $p=0.004$ ); and OS, 64% and 36% ( $p=0.005$ ). In multivariate analysis adjusting for age, stage, and tumor diameter, galectin-7 expression remained a significant predictor of DMFS (hazard ratio [HR]=0.43,  $p=0.03$ ), DSS (HR=0.34,  $p=0.001$ ), and OS (HR=0.34,  $p=0.001$ ). **CONCLUSIONS:** Elevated galectin-7 expression is associated with improved outcomes after radiation therapy for cervical cancer. Further studies are

required to validate these findings and clarify the role of galectin-7 in disease progression and radiation response.

[633]

**TÍTULO / TITLE:** - The combination of the antiviral agent cidofovir and anti-EGFR antibody cetuximab exerts an antiproliferative effect on HPV-positive cervical cancer cell lines' in-vitro and in-vivo xenografts.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Jul;24(6):599-608. doi: 10.1097/CAD.0b013e3283612a71.

●●Enlace al texto completo (gratis o de pago)

[1097/CAD.0b013e3283612a71](#)

**AUTORES / AUTHORS:** - Deberne M; Levy A; Mondini M; Dessen P; Vivet S; Supiramaniam A; Vozenin MC; Deutsch E

**INSTITUCIÓN / INSTITUTION:** - aINSERM U1030, Molecular Radiotherapy, Paris XI University bINSERM U985, Institut Gustave Roussy, le Kremlin-Bicetre cDepartment of Radiation Oncology, Institut Gustave Roussy, Villejuif, France.

**RESUMEN / SUMMARY:** - Cervical carcinoma remains a leading cause of female mortality worldwide and over 90% of these tumors contain the human papillomavirus (HPV) genome. Cross-talk between the epidermal growth factor receptor and HPV has been reported and is implicated in tumor progression. The combination of the antiviral compound cidofovir (Cd) with the monoclonal antibody anti-epidermal growth factor receptor cetuximab (Cx) was evaluated. HPV-positive (HeLa and Me180) and HPV-negative (C33A, H460 and A549) human cancer cell lines were incubated with Cd (1-10 µg/ml) and/or Cx (10 or 50 µg/ml). The antitumor effect of the combination was assessed in vitro using a clonogenic survival assay, cell cycle analysis, and phospho-H2AX level. Tumor growth delay was assayed in vivo using xenograft models. A pan-genomic analysis was carried out to identify the genes expressed differentially in untreated HeLa HPV-positive cells versus cells treated by the Cd-Cx combination. The Cd-Cx combination inhibited proliferation in all the cell lines tested. The association of Cd and Cx exerted a synergistic activity on HPV-positive but not on HPV-negative cell lines. The combination delayed tumor growth of HPV-positive tumors in vivo; however, no efficacy was reported on HPV-negative C33A xenografts nor on cell lines treated by single-drug therapy. The combination induced an S-phase arrest associated with an enhanced level of the double-strand break in Me180 and HeLa cell lines. Gene profiling assays showed a significant differential modulation of genes in HeLa cell lines treated with the combination involving the EGR-1 transcription factor. The current data support a synergistic antiproliferative action of the Cd-Cx combination on HPV-related cervical tumors.

[634]

**TÍTULO / TITLE:** - Induction of apoptosis and suppression of angiogenesis of hepatocellular carcinoma by HS-159, a novel phosphatidylinositol 3-kinase inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):201-9. doi: 10.3892/ijo.2013.1912. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1912](#)

**AUTORES / AUTHORS:** - Yun SM; Lee JH; Jung KH; Lee H; Lee S; Hong S; Hong SS

**INSTITUCIÓN / INSTITUTION:** - College of Medicine, Inha University, Jung-gu, Incheon 400-712, Republic of Korea.

**RESUMEN / SUMMARY:** - The phosphatidylinositol 3-kinase (PI3K) pathway plays a central role in cell proliferation and survival in human cancer and is emerging as an attractive therapeutic target. In this study, we synthesized a novel PI3K $\alpha$  inhibitor, HS-159 [N-(5-(3-(3-cyanophenyl)imidazo[1,2-a]pyridin-6-yl)pyridin-3-yl)benzenesulfonamide] and evaluated its anticancer effects on Huh-7 human hepatocellular carcinoma (HCC) cells. HS-159 effectively inhibited the phosphorylation of downstream PI3K effectors such as Akt, mTOR and P70S6 kinases in a dose-dependent manner. This compound also induced apoptosis and increased the fraction of apoptotic cells in the sub-G1 phase as well as the levels of cleaved PARP, caspase-3 and -9. Furthermore, HS-159 decreased the expression of hypoxia inducible factor-1 $\alpha$  and vascular endothelial growth factor which play important roles in angiogenesis. The anti-angiogenic effect of HS-159 was confirmed by the suppression of tube formation and migration of human umbilical vein endothelial cells in vitro. Collectively, our results demonstrate that HS-159 exhibited anticancer activities including the induction of apoptosis and inhibition of angiogenesis by blocking the PI3K/Akt pathway in Huh-7 cells. Therefore, we suggest that this drug may be potentially used for targeted HCC therapy.

[635]

**TÍTULO / TITLE:** - Dioscin-induced autophagy mitigates cell apoptosis through modulation of PI3K/Akt and ERK and JNK signaling pathways in human lung cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Toxicol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1007/s00204-013-1047-](#)

[Z](#)

**AUTORES / AUTHORS:** - Hsieh MJ; Tsai TL; Hsieh YS; Wang CJ; Chiou HL

**INSTITUCIÓN / INSTITUTION:** - School of Medical Laboratory and Biotechnology, Chung Shan Medical University, 110, Section 1 Chien-Kuo N. Road, Taichung, 402, Taiwan, ROC.

**RESUMEN / SUMMARY:** - Our previous study has revealed that dioscin, a compound with anti-inflammatory, lipid-lowering, anticancer and hepatoprotective effects, may induce autophagy in hepatoma cells. Autophagy is a lysosomal degradation pathway that is essential for cell survival and tissue homeostasis. In this study, the role of autophagy and related signaling pathways during dioscin-induced apoptosis in human lung cancer cells was investigated. Results from 4'-6-diamidino-2-phenylindole and annexin-V/PI double-staining assay showed that caspase-3- and caspase-8-dependent, and dose-dependent apoptoses were detected after a 24-h dioscin treatment. Meanwhile, autophagy was detected as early as 12 h after an exposure to low-dose dioscin, as indicated by an up-regulated expression of LC3-II and beclin-1 proteins. Blockade of autophagy with bafilomycin A1 or 3-methyladenine sensitized the A549 and H1299 cells to apoptosis. Treatment of A549 and H1299 cells with dioscin caused a dose-dependent increase in ERK1/2 and JNK1/2 activity, accompanied with a decreased PI3K expression and decreased phosphorylation of Akt and mTOR. Taken together, this study demonstrated for the first time that autophagy occurred earlier than apoptosis during dioscin-induced human lung cancer cell line apoptosis. Dioscin-induced autophagy via ERK1/2 and JNK1/2 pathways may provide a protective mechanism for cell survival against dioscin-induced apoptosis to act as a cytoprotective reaction.

[636]

**TÍTULO / TITLE:** - Expression of synuclein gamma indicates poor prognosis of triple-negative breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):612. doi: 10.1007/s12032-013-0612-x. Epub 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0612-](#)

[X](#)

**AUTORES / AUTHORS:** - Wu K; Huang S; Zhu M; Lu Y; Chen J; Wang Y; Lin Q; Shen W; Zhang S; Zhu J; Shi YE; Weng Z

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Xinhua Hospital Shanghai Jiaotong University School of Medicine, Shanghai, 200092, China.

**RESUMEN / SUMMARY:** - Synuclein gamma (SNCG), previously identified as breast cancer-specific gene 1, is highly expressed in malignant cells but not in normal epithelium. Studies have demonstrated that the expression of SNCG is an independent predictive marker for recurrence and metastasis in breast cancer. Triple-negative breast cancer (TNBC) is characterized by a lack of expression of both the estrogen receptor and progesterone receptor proteins as well as HER-2 and is often associated with particularly poor outcomes, early development of chemotherapy resistance, and ineffectiveness of targeted therapy. This study aimed to reveal whether SNCG-positive TNBC is more likely than SNCG-negative TNBC to have a more aggressive phenotype. One

hundred and two TNBC patients were divided into two groups according to the SNCG protein expression. Clinical and biological features of SNCG-positive tumors were compared with SNCG-negative tumors. Association between survival and SNCG expression was analyzed by the Kaplan-Meier method. Hazard ratios and 95 % confidence intervals (CIs) were calculated using Cox regression. And 34.3 % TNBCs showed moderate to strong positive SNCG expression. Patients whose tumors expressed SNCG had significantly shorter disease-free survival ( $P = 0.013$ ) and a higher probability of death ( $P = 0.002$ ) when compared with those whose tumors did not express SNCG. The hazard ratio of metastasis or recurrence based on SNCG expression status was 2.800 (95 % CI 1.193-6.574;  $P = 0.018$ ). There was no significant correlation between SNCG expression and age, lymph node involvement, and tumor stage histological type, except tumor size which was significantly associated with SNCG expression ( $P = 0.032$ ,  $R = 0.212$ ). This study suggests that SNCG expression indicates [Symbol: see text]correlates with?[Symbol: see text] a much poorer prognosis of TNBC. SNCG is expected to be a useful marker for TNBC progression and a potential target for TNBC treatment.

[637]

**TÍTULO / TITLE:** - Notch1 Contributes to Chemoresistance to Gemcitabine and Serves as an Unfavorable Prognostic Indicator in Pancreatic Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg. 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [1007/s00268-013-2010-](http://1007/s00268-013-2010-0)

[0](#)

**AUTORES / AUTHORS:** - Du X; Zhao YP; Zhang TP; Zhou L; Chen G; Cui QC; Shi J; Wang TX; You L; Shu H

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Peking Union Medical College Hospital, National Laboratory of Medical Molecular Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Pancreatic cancer (PC) carries frequent chemoresistance and extremely dismal prognosis. The underlying mechanisms remain to be further elucidated. We here report the role of Notch1 in gemcitabine resistance and its prognostic significance in PC. METHODS: A small interfering RNA (siRNA) specifically targeting Notch1 was transiently transfected into three PC cell lines (AsPC-1, BxPC-3, and MIA PaCa-2), followed by examination of chemosensitivity to gemcitabine. On the other hand, Notch1 expression was evaluated immunohistochemically and correlated with clinicopathological and prognostic variables. RESULTS: Successful knockdown of Notch1 by specific siRNA induced increased chemosensitivity to gemcitabine in all three cell lines. Immunohistochemical staining revealed that Notch1 was highly expressed in PC tissues (54.8 %), in contrast to that in para-tumor

tissues (16.4 %). In addition, Notch1 positivity was significantly correlated with early-term metastasis and shortened overall survival. Multivariate Cox regression identified Notch1 as an independent prognostic factor. CONCLUSIONS: Notch1 contributes to chemoresistance to gemcitabine, and serves as a significant indicator of unfavorable prognosis in PC.

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[638]

**TÍTULO / TITLE:** - Rapid increase of serum neuron specific enolase level and tachyphylaxis of EGFR-tyrosine kinase inhibitor indicate small cell lung cancer transformation from EGFR positive lung adenocarcinoma?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung Cancer. 2013 May 14. pii: S0169-5002(13)00152-9. doi: 10.1016/j.lungcan.2013.04.005.

●●Enlace al texto completo (gratis o de pago)

[1016/j.lungcan.2013.04.005](http://1016/j.lungcan.2013.04.005)

**AUTORES / AUTHORS:** - Zhang Y; Li XY; Tang Y; Xu Y; Guo WH; Li YC; Liu XK; Huang CY; Wang YS; Wei YQ

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Oncology, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan, China.

**RESUMEN / SUMMARY:** - We report the case of an 80-year-old male with relapsed EGFR exon 19 deletion lung adenocarcinoma treated with EGFR-tyrosine kinase inhibitor (TKI), but with poor response and rapid increase of serum neuron specific enolase (NSE). Repeat biopsy identified pathological transformation to small cell lung cancers (SCLC) retaining the same EGFR mutation. This case highlights routine serological testing of NSE may benefit for the lung adenocarcinoma patients resistant to TKIs.

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[639]

**TÍTULO / TITLE:** - Chromenylchalcones showing cytotoxicity on human colon cancer cell lines and in silico docking with aurora kinases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioorg Med Chem. 2013 May 15. pii: S0968-0896(13)00429-X. doi: 10.1016/j.bmc.2013.04.086.

●●Enlace al texto completo (gratis o de pago) [1016/j.bmc.2013.04.086](http://1016/j.bmc.2013.04.086)

**AUTORES / AUTHORS:** - Shin SY; Yoon H; Ahn S; Kim DW; Kim SH; Koh D; Lee YH; Lim Y

**INSTITUCIÓN / INSTITUTION:** - Department of Biological Sciences, College of Biological Science and Biotechnology, Konkuk University, Seoul 143-701, South Korea.

**RESUMEN / SUMMARY:** - Due to toxicity problems, various plant-derived compounds have been screened to find the chemotherapeutic agents. As

anticancer therapeutic agents, chalcones have advantages such as poor interaction with DNA and low risk of mutagenicity. Chromenones show anticancer activities too. Therefore, hybrids of chalcone and chromenone may be potent chemotherapeutic agents. We prepared 16 synthetic chromenylchalcones and applied a clonogenic long-term survival assay method for them on HCT116 human colorectal cancer cell lines. One of chromenylchalcones tested here, chromenylchalcone 11, showed IC<sub>50</sub> of 93.1nM which can be competed with the IC<sub>50</sub> values of well-known flavonoids such as catechin gallate and epicatechin gallate. Further biological experiments including cell cycle analysis, apoptosis assay, Western blot analysis, and immunofluorescent microscopy were carried out for this compound. In addition, in vitro kinases binding assay performed to explain its molecular mechanism demonstrated the compound inhibited aurora kinases. The binding modes between chromenylchalcone 11 and aurora kinases were elucidated using in silico docking experiments. These findings could be used for designing cancer therapeutic or preventive plant-derived chromenylchalcone agents.

[640]

**TÍTULO / TITLE:** - Vimentin expression predicts the occurrence of metastases in non small cell lung carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Apr 4. pii: S0169-5002(13)00116-5. doi: 10.1016/j.lungcan.2013.03.011.

●●Enlace al texto completo (gratis o de pago)

[1016/j.lungcan.2013.03.011](#)

**AUTORES / AUTHORS:** - Dauphin M; Barbe C; Lemaire S; Nawrocki-Raby B; Lagonotte E; Delepine G; Birembaut P; Gilles C; Polette M

**INSTITUCIÓN / INSTITUTION:** - INSERM UMR-S 903, SFR CAP-Sante, University of Reims-Champagne-Ardenne, 51100 Reims, France; Laboratory of Histology, CHU of Reims, 51100 Reims, France.

**RESUMEN / SUMMARY:** - Epithelial-to-mesenchymal transition (EMT) is believed to contribute to tumour invasion. Vimentin expression by carcinoma cells is a largely recognized marker of EMT. This study aimed at examining vimentin expression in non small cell lung carcinomas (NSCLC) by immunohistochemistry to evaluate potential correlations between vimentin expression and the differentiation status, the TNM stage and the outcome of the patients. 295 NSCLC including 164 squamous cell carcinomas (SCC), 108 adenocarcinomas (AC) and 23 other NSCLC carcinomas have been examined by immunohistochemistry. Vimentin was indeed detected in 145 cases (49.2%). It was principally present in isolated tumour cells and invasive clusters, particularly in cells at the tumour/stroma interface. Vimentin expression was significantly more expressed in large cell neuroendocrine, adeno-squamous and sarcomatoid carcinomas than in SCC and AC and was significantly associated

with the differentiation status of carcinomas. The follow-up of 193 patients further demonstrated that an extensive expression of vimentin (>50% of tumour cells) was associated with the occurrence of metastases. In conclusion, our data demonstrate that vimentin expression is a frequent event in NSCLC and that its expression can be associated with a lack of differentiation and the occurrence of metastases.

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[641]

**TÍTULO / TITLE:** - Prx1 modulates the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):72-8. doi: 10.3892/ijo.2013.1918. Epub 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1918](#)

**AUTORES / AUTHORS:** - Hwang KE; Park DS; Kim YS; Kim BR; Park SN; Lee MK; Park SH; Yoon KH; Jeong ET; Kim HR

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Institute of Wonkwang Medical Science, Wonkwang University, School of Medicine, Iksan, Jeonbuk 570-749, Republic of Korea.

**RESUMEN / SUMMARY:** - The expression levels of Prx1 are frequently elevated in several human cancers, including lung cancer and may confer increased resistance to treatment. In this study, we investigated the role of Prx1 in docetaxel-induced apoptosis in A549 lung cancer cells. To test whether Prx1 knockdown affected the sensitivity of A549 cells to docetaxel treatment, we generated short hairpin RNA (shRNA) constructs targeting Prx1 and analyzed the effect of Prx1 knockdown on growth and apoptosis. Tumor growth was evaluated in scrambled shRNA- or shPrx1-infected A549 cell tumors receiving docetaxel treatment. In addition, mechanistic information was gathered by western blot analysis from cell lysates of scrambled- and shPrx1-infected A549 cells pretreated with or without LY294002 and subsequently treated with docetaxel. We found that Prx1 knockdown resulted in enhanced docetaxel-induced cytotoxicity in a dose-dependent manner. In vivo, the growth rate of shPrx1-infected A549 tumors was significantly reduced compared to that of scrambled shRNA-infected A549 tumors. Prx1 knockdown also augmented the inhibitory effects of docetaxel on tumor growth. Prx1 knockdown increased the apoptotic potential through activation of the caspase cascade and suppressed docetaxel-induced phosphorylation of Akt and its substrate forkhead box O1 (FOXO1). Moreover, treatment with the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 reduced the phosphorylation of FOXO1 and increased the cytotoxicity of docetaxel in A549 cells. Our findings suggest that Prx1 may modulate the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis.

[642]

**TÍTULO / TITLE:** - Factors predictive of recurrence after surgery for gastric cancer followed by adjuvant S-1 chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1747-51.

**AUTORES / AUTHORS:** - Wada T; Kunisaki C; Hasegawa S; Takagawa R; Momiyama M; Kosaka T; Makino H; Ono HA; Oshima T; Akiyama H; Endo I

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Gastroenterological Center, Yokohama City University, Minami-ku, Yokohama, Japan.

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**RESUMEN / SUMMARY:** - BACKGROUND: The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) demonstrated that S-1(TS-1, an oral fluoropyrimidine) was effective as adjuvant chemotherapy for patients with pathological stage II or III gastric cancer who underwent curative gastrectomy. The objective of this study was to clarify the risk factors for recurrence in patients who received S-1 adjuvant chemotherapy. PATIENTS AND METHODS: We retrospectively analyzed the factors predicting recurrence in 77 patients with stage II or III gastric cancer who received S-1 chemotherapy following R0 gastrectomy between April 2003 and October 2008. RESULTS: The tumor diameter, macroscopic appearance, and presence of lymph node metastasis were significant factors predictive of recurrence identified by the univariate analysis. Moreover, the tumor diameter was an independent risk factor identified by the multivariate analysis. CONCLUSION: It is necessary to establish a chemotherapeutic regimen for patients with stage II/III gastric cancers with large tumor diameter.

[643]

**TÍTULO / TITLE:** - Hydrogen Peroxide Enhances Radiation-induced Apoptosis and Inhibition of Melanoma Cell Proliferation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):1799-807.

**AUTORES / AUTHORS:** - Fang Y; Moore BJ; Bai Q; Cook KM; Herrick EJ; Nicholl MB

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Ellis Fischel Cancer Center, University of Missouri School of Medicine, M316, Medical Sciences Building, Columbia, MO, 65212, U.S.A. [nichollm@health.missouri.edu](mailto:nichollm@health.missouri.edu) or [fangy@health.missouri.edu](mailto:fangy@health.missouri.edu).

**RESUMEN / SUMMARY:** - The efficacy of radiation therapy (RT) for melanoma is limited in part by its radioresistance. Here, we examined the radiosensitizing effect of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) on a radioresistant melanoma cell line, HTB-65. We found that H<sub>2</sub>O<sub>2</sub> synergized with RT to inhibit melanoma cell proliferation and promote apoptosis. The antiproliferative effect of H<sub>2</sub>O<sub>2</sub>/RT

correlated with increased expression of p15 and reduced expression of cyclin D, cyclin E, cyclin-dependent kinase (CDK)2 and CDK4. The pro-apoptotic effect of H<sub>2</sub>O<sub>2</sub> /RT correlated with reduced expression of the B-cell CLL/lymphoma (BCL)2. These data highlight the potential of H<sub>2</sub>O<sub>2</sub> as a radiation sensitizer for melanoma treatment and show that this warrants further study.

[644]

**TÍTULO / TITLE:** - Loss of DOK2 induces carboplatin resistance in ovarian cancer via suppression of apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 May 14. pii: S0090-8258(13)00735-X. doi: 10.1016/j.ygyno.2013.05.002.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.05.002](#)

**AUTORES / AUTHORS:** - Lum E; Vigliotti M; Banerjee N; Cutter N; Wrzeszczynski KO; Khan S; Kamalakaran S; Levine DA; Dimitrova N; Lucito R

**INSTITUCIÓN / INSTITUTION:** - Cold Spring Harbor, Woodbury, NY, United States.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Ovarian cancers are highly heterogeneous and while chemotherapy is the preferred treatment many patients are intrinsically resistant or quickly develop resistance. Furthermore, all tumors that recur ultimately become resistant. Recent evidence suggests that epigenetic deregulation may be a key factor in the onset and maintenance of chemoresistance. We set out to identify epigenetically silenced genes that affect chemoresistance. **METHODS:** The epigenomes of a total of 45 ovarian samples were analyzed to identify epigenetically altered genes that segregate with platinum response, and further filtered with expression data to identify genes that were suppressed. A tissue culture carboplatin resistance screen was utilized to functionally validate this set of candidate platinum resistance genes. **RESULTS:** Our screen correctly identified 19 genes that when suppressed altered the chemoresistance of the cells in culture. Of the genes identified in the screen we further characterized one gene, docking protein 2 (DOK2), an adapter protein downstream of tyrosine kinase, to determine if we could elucidate the mechanism by which it increased resistance. The loss of DOK2 decreased the level of apoptosis in response to carboplatin. Furthermore, in cells with reduced DOK2, the level of anoikis was decreased. **CONCLUSIONS:** We have developed a screening methodology that analyzes the epigenome and informatically identifies candidate genes followed by in vitro culture screening of the candidate genes. To validate our screening methodology we further characterized one candidate gene, DOK2, and showed that loss of DOK2 induces chemotherapy resistance by decreasing the level of apoptosis in response to treatment.

[645]

**TÍTULO / TITLE:** - Lithocholic acid-induced placental tumor necrosis factor-alpha upregulation and syncytiotrophoblast cell apoptosis in intrahepatic cholestasis of pregnancy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatol Res. 2013 Apr 30. doi: 10.1111/hepr.12150.

●●Enlace al texto completo (gratis o de pago) [1111/hepr.12150](#)

**AUTORES / AUTHORS:** - Du Q; Zhang Y; Pan Y; Duan T

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine.

**RESUMEN / SUMMARY:** - AIM: To investigate tumor necrosis factor (TNF)-alpha expression and its relationship with serum bile acids in placental trophoblasts from patients with intrahepatic cholestasis of pregnancy (ICP). METHODS: Human placenta, including normal pregnancies (n = 10) and patients with ICP (n = 10), were collected at term and subject to TNF-alpha measurements. Bile acid-induced TNF-alpha expression and cell apoptosis were evaluated in cultured syncytiotrophoblasts in vitro. RESULTS: ICP placental trophoblasts displayed apoptotic histological abnormalities. TNF-alpha levels in ICP tissue were significantly greater than those of controls as measured by quantitative polymerase chain reaction and western blot. Levels of placental TNF-alpha mRNA were positively correlated with serum bile acid concentration in ICP patients. In vitro, lithocholic acid (LCA) significantly enhanced TNF-alpha mRNA at both doses, by 2.07-fold at 15 μm and by 3.41-fold at 30 μm, whereas deoxycholic acid mildly increased TNF-alpha mRNA by 1.41-fold at 100 μm only. LCA treatment produced significantly higher percentage of caspase-3 positive cells than vehicle treatment, rescuable by the addition of a TNF-alpha inhibitor, indicative of apoptosis induced by LCA-TNF-alpha pathway. CONCLUSION: This study shows that the increase of TNF-alpha expression in placental trophoblasts is strongly associated with ICP pathology and is inducible by LCA in vitro, suggesting its potential value in the clinical prevention, diagnosis and treatment of ICP.

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[646]

**TÍTULO / TITLE:** - Interleukin-24 Induces Neuroblastoma SH-SY5Y Cell Differentiation, Growth Inhibition, and Apoptosis by Promoting ROS Production.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Interferon Cytokine Res. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1089/jir.2013.0004](#)

**AUTORES / AUTHORS:** - Li Y; Zhang H; Zhu X; Feng D; Gong J; Han T

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Surgery, Xuzhou Children's Hospital, Xuzhou, Jiangsu, China.

**RESUMEN / SUMMARY:** - Neuroblastoma is among the most aggressive tumors that occur in childhood and infancy. The clinical prognosis of children with

advanced-stage neuroblastoma is still poor. Interleukin-24 (IL-24) is emerging as a new cytokine involved in tumor cellular proliferation, differentiation, and apoptosis and has been widely studied as a tumor inhibitor. However, little is known about this cytokine's role in neuroblastoma. In this study, we investigated the possible effects of IL-24 on inducing neuroblastoma cell differentiation, growth inhibition, and apoptosis in vitro. Our data show that IL-24 promotes neuroblastoma SH-SY5Y cell differentiation, growth inhibition, and apoptosis. Furthermore, we found that the differentiation- and apoptosis-inducing action of IL-24 depends on the accumulation of reactive oxygen species (ROS). These results suggest that IL-24 can induce neuroblastoma cell differentiation and apoptosis and may be a potential therapeutic agent for neuroblastoma.

[647]

**TÍTULO / TITLE:** - Hyaluronic acid-based nanogel-drug conjugates with enhanced anticancer activity designed for the targeting of CD44-positive and drug-resistant tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Bioconjug Chem. 2013 Apr 17;24(4):658-68. doi: 10.1021/bc300632w. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago) [1021/bc300632w](#)

**AUTORES / AUTHORS:** - Wei X; Senanayake TH; Warren G; Vinogradov SV

**INSTITUCIÓN / INSTITUTION:** - Center for Drug Delivery and Nanomedicine and Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE 68198-6025, USA.

**RESUMEN / SUMMARY:** - Many drug-resistant tumors and cancer stem cells (CSC) express elevated levels of CD44 receptor, a cellular glycoprotein binding hyaluronic acid (HA). Here, we report the synthesis of nanogel-drug conjugates based on membranotropic cholesteryl-HA (CHA) for efficient targeting and suppression of drug-resistant tumors. These conjugates significantly increased the bioavailability of poorly soluble drugs with previously reported activity against CSC, such as etoposide, salinomycin, and curcumin. The small nanogel particles (diameter 20-40 nm) with a hydrophobic core and high drug loads (up to 20%) formed after ultrasonication and demonstrated a sustained drug release following the hydrolysis of biodegradable ester linkage. Importantly, CHA-drug nanogels demonstrated 2-7 times higher cytotoxicity in CD44-expressing drug-resistant human breast and pancreatic adenocarcinoma cells compared to that of free drugs and nonmodified HA-drug conjugates. These nanogels were efficiently internalized via CD44 receptor-mediated endocytosis and simultaneous interaction with the cancer cell membrane. Anchoring by cholesterol moieties in the cellular membrane after nanogel unfolding evidently caused more efficient drug accumulation in cancer cells compared to that in nonmodified HA-drug conjugates. CHA-drug nanogels were able to penetrate multicellular cancer spheroids and displayed a higher cytotoxic effect in the

system modeling tumor environment than both free drugs and HA-drug conjugates. In conclusion, the proposed design of nanogel-drug conjugates allowed us to significantly enhance drug bioavailability, cancer cell targeting, and the treatment efficacy against drug-resistant cancer cells and multicellular spheroids.

[648]

**TÍTULO / TITLE:** - MicroRNA-520c-3p inhibits hepatocellular carcinoma cell proliferation and invasion through induction of cell apoptosis by targeting glypican-3.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hepatol Res. 2013 Apr 1. doi: 10.1111/hepr.12121.

●●Enlace al texto completo (gratis o de pago) [1111/hepr.12121](#)

**AUTORES / AUTHORS:** - Miao HL; Lei CJ; Qiu ZD; Liu ZK; Li R; Bao ST; Li MY

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, The First Clinical Medical School of Jinan University, Guangzhou, China; Department of Hepatobiliary Surgery, Affiliated Hospital of Guangdong Medical College, Zhanjiang, China.

**RESUMEN / SUMMARY:** - AIM: Glypican-3 (GPC3) is a membrane-associated heparan sulfate proteoglycan involved in regulation of cell proliferation, cell survival, cell migration and differentiation process. MicroRNAs (miRNAs) are single-stranded, non-coding functional RNAs that are important in many biological processes. GPC3 and miRNAs have been found to play essential roles in the development and progression of hepatocellular carcinoma (HCC). However, little information about the relationship between GPC3 and miRNAs is available nowadays. Therefore, this study aims to examine the relationship between GPC3 and miRNAs. METHODS: Dual-luciferase reporter assay was used to validate the direct target of GPC3. Fluorescence quantitative PCR and Western blotting were used to examine the gene expression at mRNA and protein levels. Cell apoptosis was evaluated by flow cytometric analysis and Annexin V-FITC staining. Invasion of cells was evaluated by Transwell matrigel assay. RESULTS: The results showed that miR-520c-3p could specifically target GPC3 in HCC cells. GPC3 protein levels decreased with unchanged transcription efficiency after miRNA transfection, and there was negative correlation of miR-520c-3p expression in HCC in relation to GPC3 protein levels. Moreover, miR-520c-3p not only induced HCC cell apoptosis, but also inhibited the growth and invasion of the cells. Interestingly, overexpression of GPC3 could effectively reverse apoptosis induced by miR-520c-3p transfection in HCC. CONCLUSIONS: Taken together, these results supported that miR-520c-3p may decrease GPC3 protein levels to inhibit proliferation of HCC cells. Therefore, GPC3 could be a new target for genetic diagnosis and treatment of HCC.

[649]

**TÍTULO / TITLE:** - Preoperative carcinoembryonic antigen as an outcome predictor in colon cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Surg Oncol. 2013 May 16. doi: 10.1002/jso.23352.

●●Enlace al texto completo (gratis o de pago) [1002/jso.23352](#)

**AUTORES / AUTHORS:** - Amri R; Bordeianou LG; Sylla P; Berger DL

**INSTITUCIÓN / INSTITUTION:** - Division of General Surgery & Gastrointestinal Surgery, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts.

**RESUMEN / SUMMARY:** - OBJECTIVE: Several reports have shown that certain pre-operative CEA intervals can be predictive of long-term outcomes and have subsequently implied that preoperative CEA may be useful to assess the risk of recurrence or death as a continuous number for individual cases. This analysis assesses if this hypothesis is valid after correction for confounders. METHODS: All colon cancer patients operated on at Massachusetts General Hospital from 2004 through 2011 were considered for retrospective review. Association between outcomes and preoperative CEA was measured in intervals and as a linear relationship. RESULTS: Of the 1,071 patients operated for colon adenocarcinoma, 621 (57.9%) had a preoperative CEA drawn and were included in the analysis. In models using intervals, preoperative CEA did show association with (disease-free) survival, but this was shown to be chiefly a surrogate for metastatic presentation. In linear approaches adjusted for metastatic presentation, CEA loses all correlations with metastatic disease (P = 0.84), survival (P = 0.11), survival duration (P = 0.42) and disease-free interval (P = 0.94). CONCLUSIONS: Extrapolating the predictive value of certain preoperative CEA intervals to a continuous approach for use in a case-for-case basis is unjustified. Preoperative CEA may be a useful risk estimator but has limited significance for predictions of long-term outcomes in individual cases. J. Surg. Oncol. 2013;9999:XX-XX. © 2013 Wiley Periodicals, Inc.

[650]

**TÍTULO / TITLE:** - Role of Di-allyl Disulfide, a Garlic Component in NF-kappaB Mediated Transient G2-M Phase Arrest and Apoptosis in Human Leukemic Cell-lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65(4):611-22. doi: 10.1080/01635581.2013.776090.

●●Enlace al texto completo (gratis o de pago)

[1080/01635581.2013.776090](#)

**AUTORES / AUTHORS:** - Dasgupta P; Bandyopadhyay SS

**INSTITUCIÓN / INSTITUTION:** - a Department of Biophysics, Molecular Biology and Bioinformatics , University of Calcutta , Kolkata , India.

**RESUMEN / SUMMARY:** - Diallyl disulfide (DADS), the major organosulfur component of processed garlic is very effective in chemoprevention of several types of cancers; however, its detailed mechanism is yet to be divulged. Present study shows antiproliferative activity of DADS against human leukemic cell-lines, mainly U937. DADS induced transient G2/M phase arrest, which is evident from FACS analysis. The results revealed that a significant transcriptional induction of p21 happened in early hours of treatment, which is due to increased nuclear translocation of NF-kappaB and its specific binding to p21 promoter. However, in the later hours, G2/M arrest is lost leading to apoptosis via intrinsic mitochondria-mediated pathway through generation of reactive oxygen species followed by changes in mitochondrial membrane potential. Western blots indicate release of cytochrome-c, activation of caspase-3, cleavage of PARP1, and finally decrease in bcl-2 levels. In addition, inactivation of NF-kappaB by its inhibitor BAY 11-7085 causes early onset of apoptosis without any transient G2/M arrest. Thus, in conclusion, DADS induces reversible G2/M arrest through NF-kappaB mediated pathway in human leukemic cell lines, like U937, K562, and Jurkat, lacking wild type p53. However, G2/M arrest is lost owing to the incapability of the damage repair system that leads to apoptosis.

[651]

**TÍTULO / TITLE:** - Constitutive Activation of Nuclear Factor kappaB Contributes to Cystic Fibrosis Transmembrane Conductance Regulator Expression and Promotes Human Cervical Cancer Progression and Poor Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 Jun;23(5):906-15. doi: 10.1097/IGC.0b013e318292da82.

●●Enlace al texto completo (gratis o de pago)

[1097/IGC.0b013e318292da82](#)

**AUTORES / AUTHORS:** - Wu Z; Peng X; Li J; Zhang Y; Hu L

**INSTITUCIÓN / INSTITUTION:** - \*Laboratory of Biomedical Ultrasonics/Gynecological Oncology Laboratory and daggerDepartment of Obstetrics & Gynecology, West China Second University Hospital, Sichuan University; and double daggerKey Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Chengdu, People's Republic of China.

**RESUMEN / SUMMARY:** - OBJECTIVE: Cystic fibrosis transmembrane conductance regulator (CFTR) and nuclear factor kappaB (NF-kappaB) have been known to play important roles in the development and progression of many types of cancer including cervical cancer. The study aimed to verify the relevance and significance of CFTR and NF-kappaB expressions in cervical

cancer tissues and cell lines. METHODS: The expressions of CFTR and NF-kappaB p65 were analyzed respectively by immunohistochemistry in total of 135 cervical tissue samples. The correlation to clinicopathologic characteristics and prognostic value was evaluated. The coexpression of CFTR and NF-kappaB was detected in cervical cancer cell lines. Nuclear factor kappaB signaling was inhibited by siRNA for NF-kappaB p65 and activated by stimulation of cells with interleukin beta or tumor necrosis factor alpha. RESULTS: We found both the membrane expression of CFTR and nuclear translocation of NF-kappaB p65 were progressively increased from normal cervical tissue, cervical intraepithelial neoplasm, to cervical cancer (overall R = 0.74, P < 0.001). Cystic fibrosis transmembrane conductance regulator expression and NF-kappaB activation were also positively associated with stage, histological grade, lymph node metastasis, and invasive interstitial depth. Multivariate analysis showed that coexpression of CFTR and NF-kappaB was an independent prognostic factor for survival (relative risk, 5.16; P = 0.003). Dual-immunofluorescence analysis showed CFTR and NF-kappaB were coexpressed in cervical cancer. Studies in vitro revealed that the expression levels of CFTR mRNA and protein were positively related to NF-kappaB activation. CONCLUSIONS: Cystic fibrosis transmembrane conductance regulator and NF-kappaB were coexpressed in cervical cancer, and the activation of NF-kappaB mediated the expression of CFTR. Multivariate analysis revealed that coexpression of CFTR and NF-kappaB was associated with poor prognosis in patients with cervical cancer.

[652]

**TÍTULO / TITLE:** - Use of the neo-adjuvant exemestane in post-menopausal estrogen receptor-positive breast cancer: A randomized phase II trial (PTEX46) to investigate the optimal duration of preoperative endocrine therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast. 2013 Jun;22(3):263-7. doi: 10.1016/j.breast.2013.03.002. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago)

[1016/j.breast.2013.03.002](#)

**AUTORES / AUTHORS:** - Hojo T; Kinoshita T; Imoto S; Shimizu C; Isaka H; Ito H; Imi K; Wada N; Ando M; Fujiwara Y

**INSTITUCIÓN / INSTITUTION:** - Department of Breast Surgery, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo, Japan. Electronic address: [tahojo@ncc.go.jp](mailto:tahojo@ncc.go.jp).

**RESUMEN / SUMMARY:** - PURPOSE: The optimal treatment duration time and the causal relationship between neoadjuvant endocrine therapy and clinical response are not clear. Therefore, we conducted the present study to investigate the potential benefits of neoadjuvant exemestane therapy with the goal of identifying the optimal treatment duration. METHODS: This study was

conducted at three hospitals, as a multicenter, randomized phase II trial(UMIN000005668) of pre-operative exemestane treatment in post-menopausal women with untreated primary breast cancer. Fifty-one post-menopausal women with ER-positive and/or PgR-positive invasive breast cancer were randomly assigned to exemestane for 4 months or 6 months. Clinical response, pathological response, and decisions regarding breast-conserving surgery were the main outcome measures. RESULTS: Of the 52 patients that enrolled, 51 patients underwent surgery. Of those, 26 and 25 patients had been treated with exemestane for 4 and 6 months, respectively. Treatments were performed at 3 hospitals in Japan between April 2008 and August 2010. The response rates as assessed by clinical examination were 42.3% and 48.0% for 4 and 6 months of treatment, respectively. Pathological responses (minimal response or better) were observed in 19.2% and 32.0% of patients, and breast-conserving surgery was performed on 50.0% and 48.0% of patients from the 4 and 6 month treatment groups, respectively. CONCLUSION: The results of this study demonstrate that responses were equal to 4 or 6 months of exemestane treatment. Therefore, we propose that the rates of breast-conserving surgery could be maximized by 4 months of treatment. Furthermore, in addition to using exemestane as a preoperative treatment in post-menopausal women with ER-positive breast cancer, we envision administering the drug over the long term under careful clinical supervision.

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[653]

**TÍTULO / TITLE:** - Characterization and prognostic implication of 17 chromosome abnormalities in myelodysplastic syndrome.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 Jul;37(7):769-76. doi: 10.1016/j.leukres.2013.04.010. Epub 2013 Apr 29.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.04.010](#)

**AUTORES / AUTHORS:** - Sanchez-Castro J; Marco-Betes V; Gomez-Arbones X; Arenillas L; Valcarcel D; Vallespi T; Costa D; Nomdedeu B; Jimenez MJ; Granada I; Grau J; Ardanaz MT; de la Serna J; Carbonell F; Cervera J; Sierra A; Luno E; Cervero CJ; Falantes J; Calasanz MJ; Gonzalez-Porras JR; Bailen A; Amigo ML; Sanz G; Sole F

**INSTITUCIÓN / INSTITUTION:** - Hospital Arnau de Vilanova, Lleida, España.

**RESUMEN / SUMMARY:** - The prognosis of chromosome 17 (chr17) abnormalities in patients with primary myelodysplastic syndrome (MDS) remains unclear. The revised International Prognostic Scoring System (IPSS-R) includes these abnormalities within the intermediate cytogenetic risk group. This study assessed the impact on overall survival (OS) and risk of acute myeloid leukemia transformation (AMLt) of chr17 abnormalities in 88 patients with primary MDS. We have compared this group with 1346 patients with primary MDS and

abnormal karyotype without chr17 involved. The alterations of chr17 should be considered within group of poor prognosis. The different types of alterations of chromosome 17 behave different prognosis. The study confirms the intermediate prognostic impact of the i(17q), as stated in IPSS-R. The results of the study, however, provide valuable new information on the prognostic impact of alterations of chromosome 17 in complex karyotypes.

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[654]

**TÍTULO / TITLE:** - Metastasis-related miR-185 is a potential prognostic biomarker for hepatocellular carcinoma in early stage.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Jun;67(5):393-8. doi: 10.1016/j.biopha.2013.03.022. Epub 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2013.03.022](http://1016/j.biopha.2013.03.022)

**AUTORES / AUTHORS:** - Zhi Q; Zhu J; Guo X; He S; Xue X; Zhou J; Hu B; Li H; Chen S; Zhao H; Kuang Y

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou 215006, China.

**RESUMEN / SUMMARY:** - We previously reported that miR-185 is associated with hepatocellular carcinoma (HCC) venous metastasis analysed by miRNA-array profile. The aim of this study is to further investigate the clinicopathological significance and prognostic value of miR-185 in early stage HCC. We classified 95 patients with early stage HCC into treated recurrence group (TR) and none treated recurrence group (NTR), and detected the miR-185 expression levels in TR and NTR groups. We found that low miR-185 expression correlated with more tumor recurrence (37/46), while high miR-185 level led to lower recurrence rate (17/49) ( $P < 0.05$ ). There was no direct relationship between miR-185 and clinicopathological features, including age, gender, ALT, AFP, liver cirrhosis, tumor size, tumor encapsulation, tumor differentiation ( $P > 0.05$ ). Kaplan-Meier analysis showed that low miR-185 group had a remarkable lower survival rate and shorter time to recurrence than high miR-185 group ( $P < 0.05$ ). Univariate and multivariate analysis, using Cox's proportional hazards model, also indicated that low miR-185 expression was a sensitive prognostic factor for survival and recurrence in early stage HCC ( $P < 0.05$ ). We upregulated or downregulated miR-185 expression by transfected miR-185 mimics or inhibitor into HCC cell lines, and observed the influence of miR-185 on HCC cells in vitro. Our results manifested that miR-185 could suppress the tumor cell growth and invasive ability ( $P < 0.05$ ). Therefore, miR-185 might be an effective and sensitive biomarker of HCC in early stage, and the upregulation of miR-185 might be considered to be a potentially important molecular treatment strategy for patients with HCC.

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[655]

**TÍTULO / TITLE:** - Radiological response of brain metastases to novel tyrosine kinase inhibitor lapatinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - QJM. 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1093/qjmed/hct090](#)

**AUTORES / AUTHORS:** - Ammannagari N; Ahmed S; Patel A; Bravin EN

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Bassett Medical Center, Cooperstown, NY 13326, USA.

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[656]

**TÍTULO / TITLE:** - The Effect of Gartanin, a Naturally Occurring Xanthone in Mangosteen Juice, on the mTOR Pathway, Autophagy, Apoptosis, and the Growth of Human Urinary Bladder Cancer Cell Lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65 Suppl 1:68-77. doi: 10.1080/01635581.2013.785011.

●●Enlace al texto completo (gratis o de pago)

[1080/01635581.2013.785011](#)

**AUTORES / AUTHORS:** - Liu Z; Antalek M; Nguyen L; Li X; Tian X; Le A; Zi X

**INSTITUCIÓN / INSTITUTION:** - a Department of Urology , University of California , Irvine , Orange , California , USA.

**RESUMEN / SUMMARY:** - Garcinia mangostana, often referred to as mangosteen, is a fruit grown in Southeast Asia and has been used for centuries as a local beverage and natural medicine. Its bioactive compounds, xanthones (i.e., gartanin, alpha-mangostin, etc), have reported effects on ailments ranging from skin infections and inflammation to urinary tract infections. We demonstrate that mangosteen xanthones (i.e., gartanin and alpha-mangostin) at pharmacologically achievable concentrations inhibit the growth of cancer cell lines from different stages of human urinary bladder cancer. The growth inhibitory effects of gartanin in mouse embryonic fibroblasts are at least in part dependent on the existence of p53 or TSC1. Indeed, further studies have shown that gartanin treatment of bladder cancer cell lines T24 and RT4 resulted in a marked suppression of p70S6 and 4E-BP1 expression and induction of autophagy, suggesting the inhibition of the mTOR pathway. In addition, gartanin downregulated the expression of Bcl-2 and activated the p53 pathway leading to apoptosis induction. Together, these results suggested that gartanin is a multiple targeting agent that is suitable for further study into its chemopreventive properties for human urinary bladder cancer.

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[657]

**TÍTULO / TITLE:** - Neutrophil-rich Gastric Carcinomas: Light and Electron Microscopic Study of 9 Cases with Particular Reference to Neutrophil Apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ultrastruct Pathol. 2013 May;37(3):164-70. doi: 10.3109/01913123.2013.768746. Epub 2013 May 1.

●●Enlace al texto completo (gratis o de pago)

[3109/01913123.2013.768746](#)

**AUTORES / AUTHORS:** - Caruso RA; Rigoli L; Parisi A; Fedele F; Bonanno A; Paparo D; Querci A; Crisafulli C; Branca G; Venuti A

**INSTITUCIÓN / INSTITUTION:** - Department of Human Pathology .

**RESUMEN / SUMMARY:** - Abstract The authors report 9 cases of gastric carcinomas characterized by a prominent neutrophilic infiltration of the stroma. These tumors (8 of intestinal type, 1 of diffuse type) showed a pushing growth pattern. Metastatic involvement of regional lymph nodes was seen in 5 cases. The metastatic foci were associated with heavy neutrophilia as well. There was no histologic evidence of Helicobacter pylori infection, whereas various degrees of multifocal intestinal metaplasia were present in the background mucosa. Based on histologic and histochemical results, there were no apparent causes due to other infectious agents responsible for the neutrophil-rich gastric carcinomas. Some of intraepithelial and stromal neutrophils exhibited apoptotic changes, such as chromatin condensation and cell shrinkage, and were TUNEL-positive. Electron microscopy disclosed apoptotic neutrophils in cytoplasmic vacuoles of tumor cells, a finding suggestive of neutrophil-tumor cell phagocytosis (cannibalism). Different stages of neutrophil apoptosis were also shown by electron microscopy and the ultrastructural findings were compared to those described in experimental models, both in vivo and in vitro.

[658]

**TÍTULO / TITLE:** - Morusin inhibits human cervical cancer stem cell growth and migration through attenuation of NF-kappaB activity and apoptosis induction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cell Biochem. 2013 Jul;379(1-2):7-18. doi: 10.1007/s11010-013-1621-y. Epub 2013 Mar 31.

●●Enlace al texto completo (gratis o de pago) [1007/s11010-013-1621-](#)

[y](#)

**AUTORES / AUTHORS:** - Wang L; Guo H; Yang L; Dong L; Lin C; Zhang J; Lin P; Wang X

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Geriatrics, State Key Laboratory of Biotherapy, West China Hospital, West China Clinical Medical School, Sichuan University, Chengdu, 610041, China.

**RESUMEN / SUMMARY:** - Cancer stem cells (CSCs) are believed to be responsible for tumor metastasis, recurrence, and high mortality of cancer

patients due to their high tumorigenicity resistance to chemo-radiotherapy. Morusin possesses anti-cancer activity through attenuation of NF-kappaB activity, which is up-regulated in cancer stem cells. The purpose of this study is to confirm the growth and migration inhibition effect of morusin on human cervical CSCs, and to clarify its partial mechanism of activity. Human cervical CSCs were enriched using non-adhesive culture system. Their stemness characteristics were identified with tumor sphere formation, self-renewal, toluidine blue staining, migration assays, RT-PCR analysis, and immunofluorescence staining of putative stem cell markers, Oct4, SOX2, and ALDH1; the epithelial-to-mesenchymal (EMT) transition markers and relevant transcription factors were evaluated with Western blotting. The growth and migration inhibition effects of morusin on human cervical CSCs were tested by cell proliferation, tumor sphere formation, and transwell assay; apoptotic death of human cervical CSCs in response to morusin was measured with DAPI staining, apoptotic DNA fragmentation; NF-kappaBp65, Bcl-2, Bax, and caspase-3 protein expressions were detected through Western blotting. Under this non-adhesive culture system, typical tumor spheres appeared within 5-7 days, the tumor sphere formation, self-renewal, and cell migration, expressions of putative stem cell markers, EMT markers, and relevant transcription factors of the tumor sphere cells were increased significantly. After morusin treatment, the proliferation, tumor sphere formation, and migration of human cervical CSCs were decreased significantly, DAPI-stained apoptotic cells increased, apoptotic DNA fragmentations formed evidently; the expression levels of NF-kappaBp65 and Bcl-2 decreased significantly, Bax, and caspase-3 increased significantly in a dose-dependent manner. Using the non-adhesive culture system, human cervical CSCs were enriched and expanded. Morusin has the potential to target and kill CSCs, and can inhibit human cervical growth and migration through NF-kappaB attenuation mediated apoptosis induction.

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[659]

**TÍTULO / TITLE:** - Wif1 hypermethylation as unfavorable prognosis of non-small cell lung cancers with EGFR mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cells. 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1007/s10059-013-0060-7](#)

**AUTORES / AUTHORS:** - Lee SM; Park JY; Kim DS

**INSTITUCIÓN / INSTITUTION:** - Department of Anatomy, Kyungpook National University, Daegu, 702-422, Korea.

**RESUMEN / SUMMARY:** - Lung cancer is a leading cause of cancer-related mortality across the world and tobacco smoking is the major risk factor. The Wnt signaling pathway is known to be involved in smoke-induced tumorigenesis in the lung. Promoter hypermethylation of Wnt inhibitory factor 1 (Wif1) has

become a common event in a number of human tumors. Using a methylation-specific PCR, hypermethylation of the Wif1 gene promoter was evaluated in 139 primary non-small cell lung cancers (NSCLCs) and its correlation with clinicopathological and prognostic parameters was evaluated. Methylation of Wif1 was observed in 47.5% and 20.9% of neoplastic and adjacent normal lung tissues, respectively. Its methylation rate tended to be higher in stage I than stages II-III A. Results of Kaplan-Meier analysis showed no significant difference in overall survival according to Wif1 methylation status. However, Wif1 methylation showed an association with unfavorable prognosis of adenocarcinoma (AC) patients with EGFR mutation. According to our current findings, Wif1 promoter methylation is an early, frequent event as an epigenetic field manner and could be considered as a useful prognostic marker for AC patients with EGFR mutation. Further investigation into the therapeutic potential of this finding is warranted.

[660]

**TÍTULO / TITLE:** - Numbl like regulates proliferation, apoptosis, and invasion of lung cancer cell.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 17.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-0835-](#)

[7](#)

**AUTORES / AUTHORS:** - Yingjie L; Jian T; Changhai Y; Jingbo L

**INSTITUCIÓN / INSTITUTION:** - Department of Cardio-thoracic Surgery, First Affiliated Hospital of Chinese PLA General Hospital, Beijing, 100048, People's Republic of China.

**RESUMEN / SUMMARY:** - Numbl like (Numbl), a conserved homolog of Drosophila Numb, has been proved to be implicated in early development of the nervous system. A recent study also showed that Numbl played an important role in tumorigenesis and invasion by suppressing NF-kappaB activation. However, the biological role of Numbl remains unknown in lung cancer up to now. To address the expression of Numbl in the lung cancer cell, four lung cancer cell lines (metastatic cell lines NCI-H292, 95-D, and non-metastatic cell lines A549, HCC827) and non-cancerous human bronchial epithelial cells were used to detect the protein expression of Numbl by western blotting. The results in this study indicated that the expression of Numbl was downregulated in human lung cancer cell lines, especially in metastatic cell lines. To investigate the role of Numbl in lung cancer cell proliferation, apoptosis, and invasion, we generated human lung cancer 95-D cell lines in which Numbl was either overexpressed or depleted. Subsequently, the effects of Numbl on the cell viability, cycle, apoptosis, and invasion properties in 95-D cells were determined with MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay, flow cytometry analysis, and Transwell invasion assays. The results indicated that

Numbl could decrease cell viability, suppress cell proliferation and invasion, and promote cell apoptosis. In addition, we investigated the effects of Numbl on the expression of the following proteins: TRAF6 (tumor necrosis factor receptor-associated factor 6), p-p65 (phosphor-NF-kappaB), cyclin D1, caspase-3, and matrix metalloproteinase 9 (MMP9). Results showed that Numbl could decrease the expression of TRAF6, p-p65, cyclin D1, and MMP9 and increase the expression of caspase-3. All these results suggested that Numbl might be involved in the inhibition of growth, proliferation, and invasion of 95-D cells, as well as the potentiation of apoptosis of 95-D cells by abrogating TRAF6-induced activation of NF-kappaB.

[661]

**TÍTULO / TITLE:** - DLC1 as a regulator of proliferation, invasion, cell cycle, and apoptosis in cutaneous squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 28.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0813-0](http://1007/s13277-013-0813-0)

**AUTORES / AUTHORS:** - Yang C; Wu D; Jia J; Liu D; Li Z; Zhang C; Li M; Xia Y  
**INSTITUCIÓN / INSTITUTION:** - Department of Oral and Maxillofacial Surgery, The First Affiliated Hospital of Xinxiang Medical University, Weihui, Henan, 453100, China.

**RESUMEN / SUMMARY:** - Increasing evidence has demonstrated that the tumor suppressor gene deleted in liver cancer-1 (DLC1) is tightly implicated in the development and progression of tumors and is verified to be downregulated in a variety of tumors. However, the roles and precise molecular mechanisms of DLC1 in cutaneous squamous cell carcinoma (cutaneous SCC) remain to be elucidated. In the present study, we confirmed the reduced level in cutaneous SCC tissues and cells, and DLC1 mRNA relative level in cutaneous SCC tissues with lymph node metastasis (0.801 +/- 0.079) was markedly lower than those without lymph node metastasis (1.245 +/- 0.071) (P < 0.0001). Importantly, the survival rates of patients with low DLC1 level were lower than those with high DLC1 level (P = 0.0051). Further investigation revealed that DLC1 overexpression inhibited proliferation and arrested cell cycle at G0/G1 phase in A431 cells, which may be tightly associated with upregulation of p21 protein and downregulation of cyclin D1 and cdk2 proteins. Moreover, the decreases of FAK and p-FAK as well as the increase of E-cadherin level mediated by elevated DLC1 level suppressed invasion in A431 cells. Additionally, DLC1 overexpression induced apoptosis coupled with elevations of Bax level and caspase-3 activity and decrease of Bcl-2 level in A431 cells. Taken altogether, our data presented herein suggest that DLC1 plays a pivotal role in the development and progression of cutaneous SCC, which may be in

part achieved by regulating the signaling pathway related to proliferation, invasion, cell cycle, and apoptosis in cutaneous SCC cells.

[662]

**TÍTULO / TITLE:** - Anti-cancer effect of HS-345, a new tropomyosin-related kinase A inhibitor, on human pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Apr 13. pii: S0304-3835(13)00322-4. doi: 10.1016/j.canlet.2013.04.002.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.04.002](#)

**AUTORES / AUTHORS:** - Seo JH; Jung KH; Son MK; Yan HH; Ryu YL; Kim J; Lee JK; Hong S; Hong SS

**INSTITUCIÓN / INSTITUTION:** - Department of Drug Development, College of Medicine, Inha University, 3-ga, Sinheung-dong, Jung-gu, Incheon 400-712, Republic of Korea.

**RESUMEN / SUMMARY:** - Tropomyosin-related kinase A (TrkA) is emerging as an important player in carcinogenic progression. TrkA overexpression, which is associated with cell growth, proliferation, survival, and invasion, has been observed in pancreatic cancer. We therefore synthesized HS-345, a novel TrkA inhibitor, and evaluated its anti-cancer effect and underlying mechanism of action in pancreatic cancer. In this study, HS-345 effectively inhibited the growth and proliferation in three pancreatic cancer cell lines (PANC-1, MIA PaCa-2, and BxPC-3). Activation of the TrkA/Akt signal cascade was also inhibited by HS-345 treatment in a dose-dependent manner. The pro-apoptotic effect of HS-345 was evidenced by increased levels of cleaved caspase-3 and cleaved PARP, and decrease of Bcl/Bax expression via mitochondria membrane potential, as well as elevated numbers of TUNEL-positive apoptotic cells. HS-345 was additionally found to exert anti-angiogenic effect by decreasing the expression of HIF-1alpha and VEGF, major factors of angiogenesis, which were also demonstrated by the suppression of tube formation and migration of VEGF-treated human umbilical vein endothelial cells along with inhibition of blood vessel formation by HS-345 in a Matrigel plug assay with mice. Results of our investigation show that HS-345 inhibited the TrkA/Akt signaling pathway resulting in cell growth/angiogenesis inhibition and apoptosis induction. Based on our data, we suggest that HS-345 is a potential candidate for treating pancreatic cancer.

[663]

**TÍTULO / TITLE:** - Curcumin acts anti-proliferative and pro-apoptotic in human meningiomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurooncol. 2013 May 11.

●●Enlace al texto completo (gratis o de pago) [1007/s11060-013-1148-9](http://1007/s11060-013-1148-9)

**AUTORES / AUTHORS:** - Curic S; Wu Y; Shan B; Schaaf C; Utpadel D; Lange M; Kuhlen D; Perone MJ; Arzt E; Stalla GK; Renner U

**INSTITUCIÓN / INSTITUTION:** - Max Planck Institute of Psychiatry, Clinical Neuroendocrinology Group, Kraepelinstr. 10, 80804, Munich, Germany.

**RESUMEN / SUMMARY:** - Meningiomas, the most frequent benign intracranial and intraspinal types of tumors are normally removed by surgery. Complications can occur when the tumor is critically localized and cannot be completely removed or when comorbidities of the mostly elder patients increase the general surgical risk. Thus, alternate medical treatment concepts for the therapy of meningiomas would be desirable. Curcumin, the active ingredient of the spice plant *Curcuma longa* has shown anti-tumorigenic actions in many different types of tumors and therefore, its effect on growth and apoptosis of meningioma cells was studied in the present paper. In vitro, treatment of the human Ben-Men-1 meningioma cell line and of a series of 21 primary human meningioma cell cultures with curcumin (1-20  $\mu\text{M}$ ) strongly reduced the proliferation in all cases in a dose dependent manner. Cell cycle analysis by fluorescence-activated cell sorting showed growth arrest at G2/M phase, which was confirmed by demonstrating the corresponding modulation of proteins involved in G2/M arrest by immunoblotting and/or confocal laser microscopy. High dosages (20, 50  $\mu\text{M}$ ) of curcumin induced a significant increase of apoptosis in Ben-Men-1 and primary meningioma cell cultures as demonstrated by morphological changes of cell nuclei, DNA fragmentation, translocation of cell membrane associated phosphatidyl serine and the induction of apoptotic-acting cleaved caspase-3. Our results suggest that the multi-targeting drug curcumin has potent anti-tumorigenic actions in meningioma cells and might therefore be a putative candidate for the pharmacological treatment of meningiomas.

[664]

**TÍTULO / TITLE:** - Dual PI3K/mTOR inhibitor NVP-BEZ235-induced apoptosis of hepatocellular carcinoma cell lines is enhanced by inhibitors of autophagy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Jun;31(6):1449-56. doi: 10.3892/ijmm.2013.1351. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1351](http://3892/ijmm.2013.1351)

**AUTORES / AUTHORS:** - Chang Z; Shi G; Jin J; Guo H; Guo X; Luo F; Song Y; Jia X

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Beihua Affiliated Hospital, Jilin, People's Republic of China.

**RESUMEN / SUMMARY:** - Dysregulation of the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling has been found

in several types of human cancer, including hepatocellular carcinoma (HCC). NVP-BEZ235 is a novel, orally bioavailable dual PI3K/mTOR inhibitor that has exhibited promising activity against HCC in preclinical models. Autophagy is a cellular lysosomal degradation pathway essential for the regulation of cell survival and death to maintain homeostasis. This process is negatively regulated by mTOR signaling and often counteracts the efficacy of certain cancer therapeutic agents. In this study, we explored the role of autophagy in apoptosis induced by NVP-BEZ235 in two HCC cell lines, Hep3B and PLC/PRF/5, and identified the mechanism of combinatorial treatment. NVP-BEZ235 was effective in inhibiting the growth of the two HCC cell lines possibly through induction of apoptosis. NVP-BEZ235 also potently increased the expression of LC3-II and decreased the expression of p62, indicating induction of autophagy. When NVP-BEZ235 was used in combination with Atg5 siRNA or the autophagy inhibitor 3-methyladenine (3-MA), enhancement of the inhibitory effects on the growth of HCC cells was detected. In addition, enhanced induction of apoptosis was observed in cells exposed to the combination of NVP-BEZ235 and Atg5 siRNA or 3-MA. Thus, induction of autophagy by NVP-BEZ235 may be a survival mechanism that counteracts its anticancer effects. Based on these data, we suggest a strategy to enhance the anticancer efficacy of BEZ235 by blockade of autophagy. Thus, our study provides a rationale for the clinical development of combinations of NVP-BEZ235 and autophagy inhibitors for the treatment of HCC and other malignancies.

[665]

**TÍTULO / TITLE:** - Cysteine cathepsins are not critical for TRAIL- and CD95-induced apoptosis in several human cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biol Chem. 2012 Dec;393(12):1417-31.

**AUTORES / AUTHORS:** - Spes A; Sobic B; Turk V; Turk B

**INSTITUCIÓN / INSTITUTION:** - J. Stefan Institute, Department of Biochemistry and Molecular and Structural Biology, Jamova 39, SI-1000 Ljubljana, Slovenia.

**RESUMEN / SUMMARY:** - The potential role of cysteine cathepsins in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L)- and CD95 (Fas/APO-1)-induced apoptosis was investigated using four different cell lines (HeLa, HuH-7, Jurkat, and U-937). All four cell lines exhibited different levels of cathepsins and responded differently to apoptosis triggering, with Jurkat cells being the most sensitive and the only ones that were sensitive to the agonistic anti-APO-1 antibody. Apoptosis was accompanied by caspase activation, loss of the mitochondria and lysosome integrity, and the release of cysteine cathepsins into the cytosol, as judged based on the hydrolysis of the cysteine cathepsin substrate benzyloxycarbonyl-Phe-Arg-7-amino-4-methylcoumarin and by the immunological detection of cathepsin B. The inhibition of caspases by the broad-spectrum inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone

prevented apoptosis, including the mitochondrial and lysosomal membrane permeabilization, as well as cathepsin release into the cytosol, consistent with caspases playing a crucial role in the process. Conversely, however, although the broad-spectrum cysteine cathepsin inhibitor (2 S ,3 S )-trans -epoxysuccinyl-leucyl amido-3-methyl-butane ethyl ester and the more cathepsin B-selective inhibitor[(2 S ,3 S )-3-propylcarbamoxyloxirane-2-carbonyl]-l-isoleucyl-l-proline methyl ester completely blocked cathepsin activity, these inhibitors neither prevented apoptosis including the mitochondrial and lysosomal membrane permeabilization, as well as cathepsin release into the cytosol, consistent with caspases playing a crucial role in the process. Conversely, however, although the broad-spectrum cysteine cathepsin inhibitor (2 S ,3 S )-trans -epoxysuccinyl-leucylamido-3-methyl-butane ethyl ester and the more cathepsin B-selective inhibitor[(2 S ,3 S )-3-propylcarbamoxyloxirane-2-carbonyl]-l-isoleucyl-l-proline methyl ester completely blocked cathepsin activity, these inhibitors neither prevented apoptosis and its progression nor the mitochondrial and lysosomal membrane permeabilization associated with this type of cell death. Consequently, cathepsin release into the cytosol was also not prevented. Together, these data indicate that cysteine cathepsins are not required for the TRAIL- and CD95-mediated apoptosis in various human cancer cell lines. This does not, however, rule out that lysosomes and cysteine cathepsins are involved in the amplification, but not in the initiation, of death receptor-mediated apoptosis in certain cell lines or under different stimulation conditions than the ones employed here.

[666]

**TÍTULO / TITLE:** - Thickness of superficial basal cell carcinoma predicts imiquimod efficacy, a proposal for thickness-based definition of superficial basal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Br J Dermatol. 2013 Apr 30. doi: 10.1111/bjd.12402.

●●Enlace al texto completo (gratis o de pago) [1111/bjd.12402](#)

**AUTORES / AUTHORS:** - McKay KM; Sambrano BL; Fox PS; Bassett RL; Chon S; Prieto VG

**INSTITUCIÓN / INSTITUTION:** - Departments of Dermatology and Pathology, The University of Alabama at Birmingham, Birmingham, AL.

**RESUMEN / SUMMARY:** - BACKGROUND: Basal cell carcinoma (BCC) is the most common malignancy in Caucasians. It is an important driver of health care costs and causes significant morbidity. Topical imiquimod is a good non-invasive treatment alternative for surgical excision in superficial BCC (sBCC). However, there are currently no uniform histological definitions of sBCC. A definition based on tumour thickness might be a good alternative.

**OBJECTIVES:** To determine whether tumour thickness in sBCC is a predictor of treatment failure. **METHODS:** We retrospectively examined 127 histological

biopsy specimens of sBCC treated primarily with imiquimod 5 times a week for 6 weeks. Mean follow-up was 34 months (range 3-91). Recurrence was evaluated clinically with histological verification. RESULTS: Among non-recurrent cases the median tumour thickness was 0.26 millimeters (0.09 - 0.61), while for recurrent cases the median tumour thickness was 0.57 millimeters (0.41 - 1.41,  $p < 0.0001$ ). Among lesions  $\leq 0.40$  millimeters in thickness, none recurred whereas for lesions  $> 0.40$  millimeters the recurrence rate was 58% ( $p < 0.0001$ ). CONCLUSIONS: We recommend the use of tumor thickness to define superficial pattern in pathology reports for BCC as this can help to determine treatment response of sBCC to imiquimod. This article is protected by copyright. All rights reserved.

[667]

**TÍTULO / TITLE:** - Cholic acid-functionalized nanoparticles of star-shaped PLGA-vitamin E TPGS copolymer for docetaxel delivery to cervical cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomaterials. 2013 Aug;34(25):6058-67. doi: 10.1016/j.biomaterials.2013.04.052. Epub 2013 May 18.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biomaterials.2013.04.052](#)

**AUTORES / AUTHORS:** - Zeng X; Tao W; Mei L; Huang L; Tan C; Feng SS

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, Tsinghua University, Beijing 100084, PR China; The Ministry-Province Jointly Constructed Base for State Key Lab-Shenzhen Key Laboratory of Chemical Biology, the Shenzhen Key Lab of Gene and Antibody Therapy, and Division of Life and Health Sciences, Tsinghua University Shenzhen Graduate School, Shenzhen 518055, PR China.

**RESUMEN / SUMMARY:** - We developed a system of nanoparticles (NPs) of cholic acid functionalized, star-shaped block copolymer consisting of PLGA and vitamin E TPGS for sustained and controlled delivery of docetaxel for treatment of cervical cancer, which demonstrated superior in vitro and in vivo performance in comparison with the drug-loaded PLGA NPs and the linear PLGA-b-TPGS copolymer NPs. The star-shaped block copolymer CA-PLGA-b-TPGS of three branch arms was synthesized through the core-first approach and characterized by  $^1\text{H}$  NMR, GPC and TGA. The drug- or coumarin 6-loaded NPs were prepared by a modified nanoprecipitation technique and then characterized in terms of size and size distribution, surface morphology and surface charge, drug encapsulation efficiency, in vitro release profile and physical state of the encapsulated drug. The CA-PLGA-b-TPGS NPs were found to have the highest cellular uptake efficiency, the highest antitumor efficacy compared with PLGA-b-TPGS NPs and PLGA NPs. The results suggest that such a star-shaped copolymer CA-PLGA-b-TPGS could be used as a new molecular biomaterial for drug delivery of high efficiency.

[668]

**TÍTULO / TITLE:** - Identification of integrin beta1 as a prognostic biomarker for human lung adenocarcinoma using 2D-LCMS/MS combined with iTRAQ technology.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):341-9. doi: 10.3892/or.2013.2477. Epub 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2477](#)

**AUTORES / AUTHORS:** - Zhang PF; Zeng GQ; Yi LZ; Liu JP; Wan XX; Qu JQ; Li JH; Li C; Tang CE; Hu R; Ye X; Chen Y; Chen ZC; Xiao ZQ

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China.

**RESUMEN / SUMMARY:** - To discover novel lung adenocarcinoma (AdC) biomarkers, isobaric tags for relative and absolute quantitation (iTRAQ)-tagging combined with 2D-LC-MS/MS analysis was used to identify differentially expressed plasma membrane proteins in lung AdC and paired paraneoplastic normal lung tissues (PNLTs) adjacent to tumors. In this study, significant caveolin-1 downregulation and integrin beta1 upregulation was observed in primary lung AdC vs. PNL. As there has been no report on the association of integrin beta1 with lung AdC, immunohistochemical staining was performed to detect the expression of integrin beta1 in an independent set of archival tissue specimens including 42 cases of PLNT, 46 cases of without lymph node metastasis primary AdC (non-LNM AdC) and 62 cases of LNM AdC; the correlation of their expression levels with clinicopathological characteristics and clinical outcomes were evaluated. Based on the data, upregulation of integrin beta1 was significantly correlated with advanced clinical stage and lymph node metastasis. Integrin beta1 overexpression was significantly associated with advanced clinical stage ( $P<0.05$ ), lymph node metastasis ( $P<0.05$ ), increased relapse rate ( $P<0.05$ ) and decreased overall survival ( $P<0.05$ ) in AdCs. Cox regression analysis indicated that integrin beta1 overexpression is an independent prognostic factor. The data suggest that integrin beta1 is a potential biomarker for LNM and prognosis of AdC and integrin beta1 upregulation may play an important role in the pathogenesis of AdC.

[669]

**TÍTULO / TITLE:** - Icotinib, a potent and specific EGFR tyrosine kinase inhibitor, inhibits growth of squamous cell carcinoma cell line A431 through negatively regulating AKT signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Jun;67(5):351-6. doi: 10.1016/j.biopha.2013.03.012. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago)

[1016/j.biopha.2013.03.012](http://1016/j.biopha.2013.03.012)

**AUTORES / AUTHORS:** - Gao Z; Chen W; Zhang X; Cai P; Fang X; Xu Q; Sun Y; Gu Y

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

**RESUMEN / SUMMARY:** - Icotinib is a potent and specific epidermal growth factor receptor tyrosine kinase inhibitor. In this study, we reported that icotinib had the antitumor activity on human squamous cell carcinoma cell line A431 in vitro. Meanwhile, adhesion to fibronectin and expression of integrin alpha3 and beta1 were significantly reduced in a dose-dependent manner after the treatment of icotinib. Moreover, icotinib induced cell cycle arrested and affected expression of various cell cycle related proteins in squamous cancer cell line A431, whereas it did not cause apoptosis. Furthermore, icotinib remarkably down-regulated phosphorylation of protein kinase B (AKT) through blocking the interaction between 3-phosphoinositide-dependent protein kinase-1 (PDK1) and AKT in A431 cells. Taken together, it is shown that the small molecular compound, icotinib, has an anti-squamous cell carcinoma activity in vitro and its antitumor mechanism is associated with the blockage of the interaction between PDK1 and AKT. These results provide a novel strategy for anti-squamous cell carcinoma therapy.

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[670]

**TÍTULO / TITLE:** - Influence of MLH1 on colon cancer sensitivity to poly(ADP-ribose) polymerase inhibitor combined with irinotecan.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Jul;43(1):210-8. doi: 10.3892/ijo.2013.1932. Epub 2013 May 8.

●●Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1932](http://3892/ijo.2013.1932)

**AUTORES / AUTHORS:** - Tentori L; Leonetti C; Muzi A; Dorio AS; Porru M; Dolci S; Campolo F; Vernole P; Lacal PM; Praz F; Graziani G

**INSTITUCIÓN / INSTITUTION:** - Department of System Medicine, University of Rome 'Tor Vergata', I-00133 Rome, Italy.

**RESUMEN / SUMMARY:** - Poly(ADP-ribose) polymerase inhibitors (PARPi) are currently evaluated in clinical trials in combination with topoisomerase I (Top1) inhibitors against a variety of cancers, including colon carcinoma. Since the mismatch repair component MLH1 is defective in 10-15% of colorectal cancers we have investigated whether MLH1 affects response to the Top1 inhibitor irinotecan, alone or in combination with PARPi. To this end, the colon cancer cell lines HCT116, carrying MLH1 mutations on chromosome 3 and HCT116 in which the wild-type MLH1 gene was replaced via chromosomal transfer

(HCT116+3) or by transfection of the corresponding MLH1 cDNA (HCT116 1-2) were used. HCT116 cells or HCT116+3 cells stably silenced for PARP-1 expression were also analysed. The results of in vitro and in vivo experiments indicated that MLH1, together with low levels of Top1, contributed to colon cancer resistance to irinotecan. In the MLH1-proficient cells SN-38, the active metabolite of irinotecan, induced lower levels of DNA damage than in MLH1-deficient cells, as shown by the weaker induction of gamma-H2AX and p53 phosphorylation. The presence of MLH1 contributed to induce of prompt Chk1 phosphorylation, restoring G2/M cell cycle checkpoint and repair of DNA damage. On the contrary, in the absence of MLH1, HCT116 cells showed minor Chk1 phosphorylation and underwent apoptosis. Remarkably, inhibition of PARP function by PARPi or by PARP-1 gene silencing always increased the antitumor activity of irinotecan, even in the presence of low PARP-1 expression.

[671]

**TÍTULO / TITLE:** - Role of microRNAs in mechanisms of glioblastoma resistance to radio- and chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochemistry (Mosc). 2013 Apr;78(4):325-34. doi: 10.1134/S0006297913040019.

●●Enlace al texto completo (gratis o de pago)

[1134/S0006297913040019](#)

**AUTORES / AUTHORS:** - Koshkin PA; Chistiakov DA; Chekhonin VP

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Nanobiotechnology, N. I. Pirogov Russian National Research Medical University, Moscow, 117997, Russia. [philipkoshkin@gmail.com](mailto:philipkoshkin@gmail.com)

**RESUMEN / SUMMARY:** - Low-grade gliomas and multiform glioblastoma are characterized by highly pronounced anaplasia, malignization, proliferation, and invasiveness; moreover, they are highly resistant to chemo- and radiotherapy. The very low efficiency of traditional approaches in the treatment of patients with glioblastomas is due to the intensive invasive growth of the tumor resulting in deep infiltration of adjacent normal perivascular and nervous tissue and formation of areas of perineural infiltration differently remote from the tumor epicenter. MicroRNAs are key posttranscriptional regulators of gene activities, and their expression is markedly increased in tumors, in particular in gliomas. MicroRNAs have been shown to promote the growth, proliferation, migration, and survival of tumor stem and non-stem cells. However, a population of microRNA possessing antitumor effects is also detected in gliomas. As a rule, the expression of antitumor microRNAs is suppressed in tumors. In this review, we consider microRNAs, their influence on radio- and chemoresistance of gliomas, and prospects for their use as specific agents in targeted therapy of gliomas. The pool of these microRNAs has distinct therapeutic value, because on use in combined therapy it can decrease the resistance of glioma tumor

stem cells to existing pharmaceuticals and improve the efficiency of radio- and chemotherapy.

[672]

**TÍTULO / TITLE:** - Glycoprotein nonmetastatic B as a prognostic indicator in small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - APMIS. 2013 May 8. doi: 10.1111/apm.12107.

●●Enlace al texto completo (gratis o de pago) [1111/apm.12107](#)

**AUTORES / AUTHORS:** - Li YN; Zhang L; Li XL; Cui DJ; Zheng HD; Yang SY; Yang WL

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatrics, The Second Affiliated Hospital, Medical School of Xi'an Jiaotong University Xi'an, Xi'an, China.

**RESUMEN / SUMMARY:** - Glycoprotein nonmetastatic melanoma B (GPNMB) is a type I transmembrane glycoprotein which is overexpressed in many tumors and seems to play a critical role in metastasis of malignant tumors. The purpose of this study was to determine GPNMB expression in small cell lung cancer (SCLC) and analyze the prognostic value in patients with SCLC. A total of 132 cases of SCLCs were analyzed immunohistochemically on tissue microarrays (TMAs). Patients were divided into weak-positive and strong-positive GPNMB groups. In addition, serum GPNMB was evaluated by enzyme-linked immunosorbent assay (ELISA). The average serum GPNMB concentration was 1054.15 +/- 363.71 pg/mL in the weak-positive group, 2611.52 +/- 457.57 pg/mL in the strong-positive group, and 427.61 +/- 273.9 pg/mL in the control. The strong-positive group showed significantly higher serum GPNMB levels than the weak-positive group and healthy control ( $p < 0.01$ ). Overall survival in the weak-positive GPNMB group was significantly longer than in the strong-positive group (27 months vs 15 months,  $p < 0.01$ ). These results suggest that the expression of GPNMB may be useful as a prognostic indicator in patients with SCLC.

[673]

**TÍTULO / TITLE:** - Resveratrol-induced apoptosis is enhanced by inhibition of autophagy in esophageal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Mar 27. pii: S0304-3835(13)00251-6. doi: 10.1016/j.canlet.2013.03.023.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canlet.2013.03.023](#)

**AUTORES / AUTHORS:** - Tang Q; Li G; Wei X; Zhang J; Chiu JF; Hasenmayer D; Zhang D; Zhang H

**INSTITUCIÓN / INSTITUTION:** - Department of Integrative Oncology, Affiliated Cancer Hospital of Shantou University Medical College, Shantou, China; Cancer Research Center, Shantou University, Shantou, China.

**RESUMEN / SUMMARY:** - The anti-cancer activity of resveratrol in human esophageal squamous cell carcinoma (ESCC) was investigated focusing on the role of autophagy and its effects on apoptotic cell death. We demonstrated that resveratrol inhibits ESCC cell growth in a dose-dependent manner by inducing cell cycle arrest at the sub-G1 phase and resulting in subsequent apoptosis. Mechanistically, resveratrol-induced autophagy in the ESCC cells is AMPK/mTOR pathway independent. Since both pharmacological and genetic inhibition of autophagy enhanced the resveratrol-induced cytotoxicity to the ESCC cells, this provided a novel strategy in potentiating the anti-cancer effects of resveratrol and other chemotherapeutic reagents in ESCC cancer treatment.

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[674]

**TÍTULO / TITLE:** - Prolonged exposure to tyrosine kinase inhibitors or early use of everolimus in metastatic renal cell carcinoma: are the two options alike?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Jun;30(2):578. doi: 10.1007/s12032-013-0578-8. Epub 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0578-](#)

[8](#)

**AUTORES / AUTHORS:** - Calvani N; Morelli F; Chiuri V; Gnoni A; Scavelli C; Fedele P; Orlando L; Maiello E; Lorusso V; Cinieri S

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Division and Breast Unit, Sen. Antonio Perrino Hospital, S.S. 7, 72100 Brindisi, Italy.

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**RESUMEN / SUMMARY:** - We retrospectively analyzed metastatic renal cell carcinoma (RCC) patients treated with 3 targeted agents. Patients started the sequence with a tyrosine kinase inhibitor (TKI), sunitinib or sorafenib, and were divided into 2 groups based on the order in which they received the other reciprocal TKI and everolimus (EVE): TKI-TKI-EVE group (n = 19) and TKI-EVE-TKI group (n = 14). Median progression-free survival (PFS) with first TKI was 13 months in the TKI-TKI-EVE group and 10 months in the TKI-EVE-TKI group. PFS with the second agent showed a trend in favor of the TKI-TKI-EVE sequence, with a median of 11 versus 6.5 months, whereas median PFS with the third agent was 6 months in both groups. Total PFS also showed a trend in favor of the TKI-TKI-EVE sequence with a median of 31 versus 23 months. Median overall survival (OS) was 38 months in both groups, with more patients receiving subsequent treatment in the TKI-EVE-TKI group. The subgroup of patients no long-term responders ( $\leq 9$  months) to first TKI showed similar outcomes irrespective of the sequence. The subgroup of long-term responders to first TKI ( $> 9$  months) who received the other TKI instead of EVE had better

outcomes in terms of median PFS with the second agent (13 vs. 5.5 months;  $p = 0.0271$ ), median total PFS (39.5 vs. 23.5 months;  $p = 0.0415$ ), and median OS (46 vs. 38 months). In conclusion, no apparent advantage was observed with early use of EVE in advanced RCC, even in those patients who did not benefit long from first-line TKI, whereas long-term duration of first-line TKI seems to be predictor of second-line TKI efficacy.

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[675]

**TÍTULO / TITLE:** - Leptin induces cell proliferation and reduces cell apoptosis by activating c-myc in cervical cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jun;29(6):2291-6. doi: 10.3892/or.2013.2390. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2390](#)

**AUTORES / AUTHORS:** - Yuan Y; Zhang J; Cai L; Ding C; Wang X; Chen H; Wang X; Yan J; Lu J

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Shaanxi Cancer Hospital, Xi'an, Shaanxi 710061, PR China.

**RESUMEN / SUMMARY:** - Leptin may be involved in the pathogenesis of numerous cancer types by activation of cellular signal-transduction pathways. In this study, we analyzed the role of leptin and the mechanism(s) underlying its action in cervical carcinoma cells. Firstly, we examined the expression of leptin in 80 cases of cervical carcinoma using immunohistochemical staining. The results showed that the levels of leptin correlated significantly with the grades of cervical carcinoma. At the same time, the expression of leptin correlated positively with c-myc and its downstream gene, bcl-2. The expression of c-myc and bcl-2 was evaluated in leptin-treated HeLa cells by reverse transcription-polymerase chain reaction (RT-PCR) and western blotting. Recombinant leptin significantly activated the expression of bcl-2 and c-myc in HeLa cells. Finally, the apoptotic index, the proliferative activity and the expression levels of c-myc and bcl-2 were determined in the HeLa cells treated with silencing of leptin. We found that silencing of leptin inhibited the proliferation of HeLa cells and reduced the expression of bcl-2 and c-myc. Our data demonstrated that leptin interferes with the expression of oncogenic c-myc and anti-apoptotic bcl-2, and regulates cell turnover and facilitates the progression of cervical cancer.

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[676]

**TÍTULO / TITLE:** - Twist2 is a valuable prognostic biomarker for colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Gastroenterol. 2013 Apr 21;19(15):2404-11. doi: 10.3748/wjg.v19.i15.2404.

●●Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i15.2404](#)

**AUTORES / AUTHORS:** - Yu H; Jin GZ; Liu K; Dong H; Yu H; Duan JC; Li Z; Dong W; Cong WM; Yang JH

**INSTITUCIÓN / INSTITUTION:** - Department of Laparoscopy, Eastern Hepatobiliary Surgery Hospital, the Second Military Medical University, Shanghai 200438, China.

**RESUMEN / SUMMARY:** - AIM: To investigate the significance of Twist2 for colorectal cancer (CRC). METHODS: In this study, 93 CRC patients were included who received curative surgery in Eastern Hepatobiliary Surgery Hospital from January 1999 to December 2010. Records of patients' clinicopathological characteristics and follow up data were reviewed. Formalin-fixed, paraffin-embedded tissue blocks were used to observe the protein expression of Twist2 and E-cadherin by immunohistochemistry. Two independent pathologists who were blinded to the clinical information performed semiquantitative scoring of immunostaining. A total score of 3-6 (sum of extent + intensity) was considered as Twist2-positive expression. The expression of E-cadherin was divided into two levels (preserved and reduced). An exploratory statistical analysis was conducted to determine the association between Twist2 expression and clinicopathological parameters, as well as E-cadherin expression. Furthermore, the variables associated with prognosis were analyzed by Cox's proportional hazards model. Kaplan-Meier analysis was used to plot survival curves according to different expression levels of Twist2. RESULTS: Twist2-positive expression was observed in 66 (71.0%) samples and mainly located in the cytoplasm. Forty-three (46.2%) samples showed reduced expression of E-cadherin. There were no significant correlations between Twist2 expression and any of the clinicopathological parameters. However, Twist2-positive expression was significantly associated with reduced expression of E-cadherin ( $P = 0.040$ ). Multivariate analysis revealed that bad M-stage [hazard ratio (HR) = 7.694, 95%CI: 2.927-20.224,  $P < 0.001$ ] and Twist2-positive (HR = 5.744, 95%CI: 1.347-24.298,  $P = 0.018$ ) were the independent risk factors for poor overall survival (OS), while Twist2-positive (HR = 3.264, 95%CI: 1.455-7.375,  $P = 0.004$ ), bad N-stage (HR = 2.149, 95%CI: 1.226-3.767,  $P = 0.008$ ) and bad M-stage (HR = 10.907, 95%CI: 4.937-24.096,  $P < 0.001$ ) were independently associated with poor disease-free survival (DFS). Survival curves showed a definite trend for Twist2-negative patients to have longer OS and DFS than Twist2-positive patients, not only overall, but also for patients in different stages, especially for DFS of patients in stage III ( $P = 0.033$ ) and IV ( $P = 0.026$ ). CONCLUSION: Our data suggests, for the first time, that Twist2 is a valuable prognostic biomarker for CRC, particularly for patients in stage III and IV.

[677]

**TÍTULO / TITLE:** - Beclin 1 and its emerging role as a prognostic biomarker in systemic malignancies besides bladder carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biol Markers. 2013 Apr 23;28(1):e113. doi: 10.5301/JBM.2013.10558.

●●Enlace al texto completo (gratis o de pago) [5301/JBM.2013.10558](#)

**AUTORES / AUTHORS:** - Kapoor S

**INSTITUCIÓN / INSTITUTION:** - Private practice, Mechanicsville, VA, USA.

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[678]

**TÍTULO / TITLE:** - Cost-Effectiveness of BRCA1 and BRCA2 Mutation Testing to Target PARP Inhibitor Use in Platinum-Sensitive Recurrent Ovarian Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 Jun;23(5):846-852.

●●Enlace al texto completo (gratis o de pago)

[1097/IGC.0b013e31829527bd](#)

**AUTORES / AUTHORS:** - Secord AA; Barnett JC; Ledermann JA; Peterson BL; Myers ER; Havrilesky LJ

**INSTITUCIÓN / INSTITUTION:** - \*Division of Gynecologic Oncology, Duke Cancer Institute, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC; daggerDivision of Gynecologic Oncology, Department of Obstetrics and Gynecology, Brooke Army Medical Center, Fort Sam Houston, TX; double daggerUCL Cancer Institute and Biomedical Research Centre, London, United Kingdom; section signDepartment of Biostatistics and Bioinformatics, and parallelDivision of Clinical and Epidemiological Research, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC.

**RESUMEN / SUMMARY:** - OBJECTIVES: (1) To determine whether use of a PARP inhibitor or (2) BRCA1/2 mutation testing followed by a PARP inhibitor for test positives is potentially cost-effective for maintenance treatment of platinum-sensitive recurrent high-grade serous ovarian cancer. METHODS: A modified Markov decision analysis compared 3 strategies: (1) observe; (2) olaparib to progression; (3) BRCA1/2 mutation testing; treat mutation carriers with olaparib to progression. Progression-free survival and rates of adverse events were derived from a phase 2 randomized trial. Key assumptions are as follows: (1) 14% of patients harbor a BRCA1/2 mutation; (2) progression-free survival of individuals treated with olaparib is improved for BCRA1/2 carriers compared with noncarriers (estimated hazard ratio, approximately 0.4). Costs derived from national data were assigned to treatments, adverse events, and BRCA1/2 test. Monte Carlo probabilistic sensitivity analysis was performed. RESULTS: Global olaparib was the most effective strategy, followed by BRCA1/2 testing and no olaparib. BRCA1/2 testing had an incremental cost-effectiveness ratio (ICER) of \$193,442 per progression-free year of life saved (PF-YLS) compared to no olaparib, whereas global olaparib had an ICER of \$234,128 per PF-YLS compared to BRCA1/2 testing. At a 52% lower-than-baseline olaparib cost

estimate of \$3000 per month, BRCA1/2 testing became potentially cost-effective compared with observation, with an ICER of \$100,000 per PF-YLS. When strategy (1) was removed from the analysis, BRCA1/2 testing was the preferred strategy. CONCLUSIONS: The use of maintenance olaparib in women with high-grade serous ovarian cancer is not cost-effective regardless of whether BRCA1/2 testing is used to direct treatment. However, BRCA1/2 testing is a preferred strategy compared to global maintenance olaparib alone.

[679]

**TÍTULO / TITLE:** - Regression of canine cutaneous histiocytoma: reduced proliferation or increased apoptosis?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Apr;33(4):1397-400.

**AUTORES / AUTHORS:** - Pires I; Alves A; Queiroga FL; Silva F; Lopes C

**INSTITUCIÓN / INSTITUTION:** - Department of Veterinary Sciences, University of Tras-os-Montes and Alto Douro, Vila Real, Portugal.

**RESUMEN / SUMMARY:** - BACKGROUND/AIM: Canine cutaneous histiocytoma (CCH) is a tumour that undergoes spontaneous regression. The aim of this study was to establish a possible relationship between regression of CCH and tumoural cell proliferation and apoptosis. MATERIALS AND METHODS: Immunostaining with Ki-67 antigen and the terminal deoxytransferase (TdT) deoxyuridine-5'-triphosphated (dUTP) nick-end labelling (TUNEL) method were performed on 93 specimens of CCH, grouped into four histological groups. RESULTS: The proliferative index evaluated with Ki-67 antigen expression was on average 23.56 +/- 7.91%. The apoptotic index determined by the TUNEL method was on average 39.37 +/- 5.87%. Neither the proliferative nor apoptotic index differed between histological groups. Moreover, the proliferative and apoptotic indices did not correlate significantly. However, apoptotic activity was higher than proliferative activity in almost all tumours. CONCLUSION: A reduction of proliferation or an increase of apoptosis does not appear to justify regression of CCH. However, our results suggest that an imbalance between cell proliferation and apoptotic cell death plays a significant role in spontaneous regression of CCH.

[680]

**TÍTULO / TITLE:** - Single-agent Smac-mimetic compounds induce apoptosis in B chronic lymphocytic leukaemia (B-CLL).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Res. 2013 Jul;37(7):809-15. doi: 10.1016/j.leukres.2013.03.016. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago)

[1016/j.leukres.2013.03.016](http://1016/j.leukres.2013.03.016)

**AUTORES / AUTHORS:** - Scavullo C; Servida F; Lecis D; Onida F; Drago C; Ferrante L; Seneci P; Barcellini W; Lionetti M; Todoerti K; Neri A; Delia D; Deliliers GL

**INSTITUCIÓN / INSTITUTION:** - Fondazione Matarrelli, Dipartimento di Farmacologia Chemioterapia e Tossicologia Medica, Università degli Studi di Milano, Milano, Italy.

**RESUMEN / SUMMARY:** - Defective apoptosis is a hallmark of the progression of B chronic lymphocytic leukaemia (B-CLL). Smac-mimetics have been shown to induce apoptosis in several tumours. We describe the in vitro pro-apoptotic activity and regulation of the molecular pathway induced by new Smac-mimetics in B-CLL. The cytotoxic effect was significantly higher in B-CLL samples than in healthy controls. No significant synergistic effect was observed in combined treatment. In conclusion one of our compounds (Smac66), used as monotherapy and not in combination, is highly active against B-CLL cells thus suggesting a promising therapeutic potential as a new class of antileukemic drugs in haematology.

[681]

**TÍTULO / TITLE:** - Effects of Rab27a on proliferation, invasion, and anti-apoptosis in human glioma cell.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0756-](http://1007/s13277-013-0756-5)

[5](#)

**AUTORES / AUTHORS:** - Wu X; Hu A; Zhang M; Chen Z

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The Second Affiliated Hospital of Anhui Medical University, 678 Furong Road, Hefei, 230061, People's Republic of China.

**RESUMEN / SUMMARY:** - This study aims to investigate the relationship between Rab27a and the characteristics of glioma cell U251 such as proliferation, apoptosis, and invasion and to provide an experimental basis for future therapy in human glioma. Recombinant plasmid of pcDNA3.1-Rab27a was constructed and transfected into U251 cells with the help of Lipofectamine2000. The expression of Rab27a was detected by Western blot. Cell viability, cell cycle, cell apoptosis, and cell migration were analyzed, respectively, by (3-(4,5)-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, flow cytometry, and Transwell invasion chamber methods. Meanwhile, the effect of Rab27a on secretion of cathepsin D in U251 cells was also examined. With the help of luciferase reporter assay system, the relationship between miR-124 and gene Rab27a expression was explored. Western blot showed that the expression of Rab27a was significantly increased in pcDNA3.1-Rab27a transfection group ( $p < 0.01$ ) and that was significantly decreased in Rab27a-shRNA transfection group ( $p < 0.01$ ) compared with control group. MTT assay,

flow cytometry, and Transwell invasion chamber experiment indicated that cell viability ( $p < 0.01$ ), proliferation index ( $p < 0.05$ ), and invasion ability ( $p < 0.01$ ) were improved significantly in pcDNA3.1-Rab27a transfection group compared with control group and that cell viability ( $p < 0.01$ ), proliferation index ( $p < 0.05$ ), and invasion ability ( $p < 0.01$ ) were reduced markedly in Rab27a-shRNA transfection group compared with control group. The apoptosis analysis by flow cytometry demonstrated that the ratio of apoptosis in pcDNA3.1-Rab27a transfection group was significantly lower than that in control group ( $p < 0.05$ ) and the ratio was notably higher in Rab27a-shRNA transfection group than that in the control group. Cathepsin D activity assay indicated that the release of cathepsin D was enhanced in pcDNA3.1-Rab27a transfection group compared to that in the control group ( $p < 0.05$ ). Rab27a could increase the glioma cell ability, promote proliferation and invasion, and suppress cell apoptosis. The above-stated effects of Rab27a possibly were exerted by increasing the secretion of cathepsin D and regulated by miR-124. In addition, the inhibition of expression of Rab27a perhaps benefited the therapy for glioma patients.

[682]

**TÍTULO / TITLE:** - Inhibition of CK2 enhances UV-triggered apoptotic cell death in lung cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):377-84. doi: 10.3892/or.2013.2407. Epub 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2407](#)

**AUTORES / AUTHORS:** - Zhao T; Jia H; Li L; Zhang G; Zhao M; Cheng Q; Zheng J; Li D

**INSTITUCIÓN / INSTITUTION:** - Jiangsu Key Laboratory of Biological Cancer Therapy, Xuzhou Medical College, Xuzhou, Jiangsu 221002, P.R. China.

**RESUMEN / SUMMARY:** - Lung cancer is a high-grade malignancy with poor 5 year-survival rates that remains incurable with current therapies. Different cellular stresses, including antitumor agents, ionizing radiation and ultraviolet (UV) light, can induce apoptosis and activate signaling pathways. UV has multiple effects on tumor cells, including DNA damage, and increases the expression of some genes involved in tumor cell apoptosis and DNA repair. It has been reported that UV can also activate casein kinase 2 (CK2). CK2, a Ser/Thr protein kinase, has been reported to be frequently overexpressed in various types of human cancer, including lung cancer, and is associated with tumor development. Thus, combination of UV and CK2 inhibitors may be a new strategy for the treatment of lung cancer. Our results demonstrated that inhibition of CK2a through CK2 siRNA or a CK2 inhibitor [(4,5,6,7-tetrabromobenzotriazole (TBB)] enhances the decrease in cell viability of lung cancer cells (A549 and H2030) induced by UV. Western blot analysis demonstrated that the combination increased the expression of apoptotic

protein markers cytochrome c and the cleavage of poly ADP-ribose polymerase (PARP) and caspase-3. Furthermore, our results indicated that UV decreased the expression of the tumor suppressor protein PML through activation of CK2. Inhibition of CK2 by CK2 siRNA and TBB can recover the reduction of PML induced by UV. Collectively, these results demonstrate the significant apoptosis of lung cancer cells induced by combination treatment of the CK2 inhibitor and UV radiation. CK2 enhanced cell apoptosis by UV radiation may due, at least partly, to recover the expression of PML. These findings warrant the clinical testing of CK2 inhibitors which, when used in conjunction with DNA-damaging agents such as radiation, may be an effective cancer therapeutic strategy.

[683]

**TÍTULO / TITLE:** - HSPA9 overexpression inhibits apoptin-induced apoptosis in the HepG2 cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jun;29(6):2431-7. doi: 10.3892/or.2013.2399. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2399](#)

**AUTORES / AUTHORS:** - Peng C; Yang P; Cui Y; He M; Liang L; Di Y

**INSTITUCIÓN / INSTITUTION:** - Clinical Laboratory of Yanan Hospital of Kunming, and Department of Biochemistry and Molecular Biology, Kunming Medical University, Kunming 650051, PR China.

**RESUMEN / SUMMARY:** - Apoptin, a small protein derived from chicken anemia virus, possesses the capacity to specifically kill tumor cells while leaving normal cells intact. Previous studies have indicated that the subcellular localization of apoptin appears to be crucial for this tumor-selective activity. Apoptin resides in the cytoplasm of normal cells; however, in cancer cells it translocates into the nucleus. In the present study, purified prokaryotic native His-apoptin served as a bait for capturing apoptin-associated proteins in both a hepatoma carcinoma cell line (HepG2) and a human fetal liver cell line (L-02). The captured proteins obtained from a pull-down assay were separated by two-dimensional gel electrophoresis. Mass spectrometry was employed to detect the effect of HSPA9 overexpression (one of the interacting proteins with apoptin in vitro) and downregulation of HSPA9 on HepG2 cells. The data revealed that HSPA9 overexpression resulted in partial distribution of apoptin in the cytoplasm. Notably, HSPA9 overexpression markedly decreased the apoptosis rate of HepG2 cells from 41.2 to 31.7%, while the downregulation of HSPA9 using small interfering RNA significantly enhanced the apoptosis of HepG2 cells. Our results suggest new insights into the localization mechanism of apoptin which is tightly associated with HSPA9 overexpression and its crucial role in cellular apoptosis both in a tumor cell line (HepG2) and a normal cell line (L-02). These findings shed new light on the elucidation of the underlying mechanism of anticancer action of apoptin.

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[684]

**TÍTULO / TITLE:** - Embelin-induced brain glioma cell apoptosis and cell cycle arrest via the mitochondrial pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jun;29(6):2473-8. doi: 10.3892/or.2013.2369. Epub 2013 Mar 29.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2369](#)

**AUTORES / AUTHORS:** - Wang A; Zhang B; Zhang J; Wu W; Wu W

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine-Neurology, Central Hospital of Nanyang, Nanyang 473009, PR China.

**RESUMEN / SUMMARY:** - Brain glioma is the most common malignant intracranial tumor and has become the focus of research on diseases of the central nervous system due to its high incidence and poor prognosis. As a smallmolecule inhibitor of X-linked inhibitor of apoptosis protein (XIAP), embelin has the ability to specifically inhibit XIAP to control and regulate the apoptosis of various types of tumor cells. However, to date, the mechanism of action for this effect is not well understood. The aim of this study was to investigate the role that the mitochondrial pathway plays in embelin-induced brain glioma cell apoptosis and the effect of embelin on the cell cycle. Brain glioma cells were treated with different doses of embelin. The MTT method was used to determine cell proliferation, and flow cytometry was used to determine apoptosis, as well as changes in the cell cycle and cell mitochondrial membrane potential. Western blot analysis was performed to determine the expression levels of apoptosisassociated proteins, Bcl-2, Bcl-xL, Bax and Bak as well as cytochrome c. We found that embelin induced a time and dosedependent apoptosis of brain glioma cells, and that it could arrest the cell cycle in the G0/G1 phase. Embelin also caused changes in brain glioma cell mitochondrial membrane potential. Additionally, embelin regulated the shifting of Bax and Bcl-2 to promote the mitochondrial release of cytochrome c, thus activating the caspase proteins to cause apoptosis. Thus, embelin induces apoptosis in brain glioma cells which is closely associated with the mitochondrial pathway.

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[685]

**TÍTULO / TITLE:** - Immunomodulatory effects of interferons in malignancies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Interferon Cytokine Res. 2013 Apr;33(4):154-61. doi: 10.1089/jir.2012.0167.

●●Enlace al texto completo (gratis o de pago) [1089/jir.2012.0167](#)

**AUTORES / AUTHORS:** - Bekisz J; Sato Y; Johnson C; Husain SR; Puri RK; Zoon KC

**INSTITUCIÓN / INSTITUTION:** - Cytokine Biology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

**RESUMEN / SUMMARY:** - Investigation of the antitumor and immunomodulatory activities of interferon (IFN) began shortly after the cytokine was discovered in 1957. Early work showed a direct correlation between administration of IFN and inhibition of symptoms associated with virally induced leukemia in mice as well as an increase in their survival time. Subsequent studies with purified IFNs confirmed the direct and indirect stimulation of immune cells, resulting in antitumor activities of IFN. Clinically, IFN- $\alpha$ s (alphas) have been shown to have activity against a variety of tumors. Initially, the U.S. Food and Drug Administration licensed 2 recombinant IFN- $\alpha$ s for the treatment of hairy-cell leukemia and then later for several other cancers. The success rate seen with IFNs and certain tumors has been varied. Unfortunately, some neoplasms show no response to IFN. Monocytes/macrophages play an important role in cancer progression. Monocytes in combination with IFN may be an important therapy for several cancers. This article focuses on the role of IFN and monocytes alone or in combination in affecting malignancies.

[686]

**TÍTULO / TITLE:** - Regulation of snoRNAs in cancer: close encounters with interferon.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Interferon Cytokine Res. 2013 Apr;33(4):189-98. doi: 10.1089/jir.2012.0106.

●●Enlace al texto completo (gratis o de pago) [1089/jir.2012.0106](http://1089/jir.2012.0106)

**AUTORES / AUTHORS:** - Nallar SC; Kalvakolanu DV

**INSTITUCIÓN / INSTITUTION:** - Department of Microbiology & Immunology, Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201, USA.

**RESUMEN / SUMMARY:** - The interferon (IFN) family of cytokines regulates many cellular processes, such as transcription, translation, post-translational modifications, and protein degradation. IFNs induce growth inhibition and/or cell death, depending on the cell type, by employing different proteins. This review describes a novel growth-suppressive pathway employed by IFNs that affects rRNA levels. Maturation of rRNA involves numerous noncoding small regulatory RNA-guided processes. These regulatory RNAs, called small nucleolar RNA (snoRNAs), function as a ribonucleoprotein particle (RNP) in the nucleolus. The biogenesis of snoRNPs is dependent on core protein and assembly factors. Our laboratory recently isolated a growth-suppressive protein gene associated with retinoid-IFN-induced mortality (GRIM)-1 using a genetic screen. IFN-inducible GRIM-1 (SHQ1) is an assembly factor that controls one arm of the snoRNP machinery. GRIM-1 inhibits sno/scaRNP formation to

induce growth suppression via reduction in mature rRNA levels. Loss of GRIM-1 observed in certain cancers implicates it to be a novel tumor suppressor. Certain snoRNAs have been reported to act as either oncogenes or tumor suppressors in vitro. Recent studies have shown that certain sno/scaRNAs are further processed into micro RNA-like molecules to control translation of protein-coding RNAs. We present a model as to how these small regulatory RNAs influence cell growth and a potential role for GRIM-1 in this process.

[687]

**TÍTULO / TITLE:** - Type I and Type II Interferons Inhibit Both Basal and Tumor Necrosis Factor-alpha-Induced CXCL8 Secretion in Primary Cultures of Human Thyrocytes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Interferon Cytokine Res. 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [1089/jir.2012.0080](http://1089/jir.2012.0080)

**AUTORES / AUTHORS:** - Rotondi M; Coperchini F; Sideri R; Gropelli G; de Martinis L; Villani L; Pignatti P; Magri F; Chiovato L

**INSTITUCIÓN / INSTITUTION:** - 1 Unit of Internal Medicine and Endocrinology, Fondazione Salvatore Maugeri I.R.C.C.S., University of Pavia, Pavia, Italy.

**RESUMEN / SUMMARY:** - Interferons (IFNs) and tumor necrosis factor-alpha (TNF-alpha) cooperate in activating several inflammation-related genes, which sustain chronic inflammation in autoimmune thyroid disease (AITD). Much is known about the positive signaling of IFNs to activate gene expression in AITD, while the mechanisms by which IFNs negatively regulate genes remain less studied. While IFNs inhibit CXCL8 secretion in several human cell types, their effects on thyroid cells were not evaluated. Our aim was to study the interplay between TNF-alpha and type I or type II IFNs on CXCL8 secretion by human thyroid cells. CXCL8 was measured in supernatants of primary cultures of thyroid cells basally and after a 24-h incubation with TNF-alpha. CXCL8 was detected in thyroid cell supernatants in basal conditions (96.2+/-23.5pg/mL) being significantly increased (784.7+/-217.3 pg/mL; P<0.0001 vs. basal) by TNF-alpha. Twenty-four hour incubation with IFN-gamma or IFN-beta or IFN-alpha dose dependently and significantly inhibited both basal and TNF-alpha-induced CXCL8 secretion. The degree of the inhibitory effect was IFN-gamma>IFN-beta>IFN-alpha. This study demonstrates that type I and type II IFNs downregulate both basal and TNF-alpha-induced CXCL8 secretion by human thyrocytes, IFN-gamma being the most powerful inhibitor. Future studies aimed at a better comprehension of the interplay between CXCL8 and thyroid diseases appear worthwhile.

[688]

**TÍTULO / TITLE:** - Increased glutamate uptake in astrocytes via propentofylline results in increased tumor cell apoptosis using the CNS-1 glioma model.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurooncol. 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1007/s11060-013-1158-](http://1007/s11060-013-1158-7)

[7](#)

**AUTORES / AUTHORS:** - Jacobs VL; De Leo JA

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth, Hanover, NH, 03755, USA, [valerie.l.jacobs.gr@dartmouth.edu](mailto:valerie.l.jacobs.gr@dartmouth.edu).

**RESUMEN / SUMMARY:** - Glioblastoma multiforme is one of the most common and aggressive primary brain tumors in adults. High glutamate levels are thought to contribute to glioma growth. While research has focused on understanding glutamate signaling in glioma cells, little is known about the role of glutamate between glioma and astrocyte interactions. To study the relationship between astrocytes and tumor cells, the CNS-1 rodent glioma cell line was used. We hypothesized increased glutamate uptake by astrocytes would negatively affect CNS-1 cell growth. Primary rodent astrocytes and CNS-1 cells were co-cultured for 7 days in a Boyden chamber in the presence of 5 mM glutamate. Cells were treated with propentofylline, an atypical synthetic methylxanthine known to increase glutamate transporter expression in astrocytes. Our results indicate astrocytes can increase glutamate uptake through the GLT-1 transporter, leading to less glutamate available for CNS-1 cells, ultimately resulting in increased CNS-1 cell apoptosis. These data suggest that astrocytes in the tumor microenvironment can be targeted by the drug, propentofylline, affecting tumor cell growth.

[689]

**TÍTULO / TITLE:** - Fengycin inhibits the growth of the human lung cancer cell line 95D through reactive oxygen species production and mitochondria-dependent apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Jul;24(6):587-98. doi: 10.1097/CAD.0b013e3283611395.

●●Enlace al texto completo (gratis o de pago)

[1097/CAD.0b013e3283611395](http://1097/CAD.0b013e3283611395)

**AUTORES / AUTHORS:** - Yin H; Guo C; Wang Y; Liu D; Lv Y; Lv F; Lu Z

**INSTITUCIÓN / INSTITUTION:** - aLaboratory of Enzyme Engineering, College of Food Science and Technology, Nanjing Agricultural University bState Key Laboratory of Natural Medicines, China Pharmaceutical University cDepartment of Microbiology, Institute of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu Province, China.

**RESUMEN / SUMMARY:** - To investigate the antitumor activity and action mechanism of fengycin using the human lung cancer cell line 95D. The antitumor activity of fengycin was tested in vitro and in vivo. Reactive oxygen species production, Ca uptake, and mitochondrial membrane potential loss induced by fengycin in 95D cells were measured by flow cytometry and a laser confocal microscope. Lactate dehydrogenase release and caspase activity in fengycin-treated 95D cells were assayed using cytotoxicity detection kits. Apoptosis triggered by fengycin was identified by 4,6-diamidino-2-phenylindole (DAPI) staining and flow cytometry. The effects of fengycin on cell-cycle and apoptosis-related proteins were evaluated by quantitative reverse-transcription PCR and western blot. Treatment with fengycin not only significantly decreased cell proliferation in various cancer cell lines including 95D but inhibited the growth of xenografted 95D cells in nude mice. Fengycin also induced reactive oxygen species production and Ca uptake, as well as lactate dehydrogenase release and mitochondrial membrane potential loss. Further experiments showed that fengycin could trigger apoptosis in 95D cells and cause cell-cycle arrest at the G0/G1 stage by downregulating cyclin D1 and cyclin-dependent kinase 4 (CDK4). While investigating caspase activity and the expression of apoptosis-related proteins, fengycin was found to induce apoptosis in 95D cells through the mitochondrial pathway, evidenced by increased caspase activity, Bax expression, and cytochrome c release into the cytoplasm, as well as decreased Bcl-2 levels. Fengycin can inhibit the growth of the cancer cell line 95D by regulating the cell cycle and promoting apoptosis, suggesting that it may have potential as an anticancer treatment.

[690]

**TÍTULO / TITLE:** - Disseminated neoplasia causes changes in ploidy and apoptosis frequency in cockles *Cerastoderma edule*.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Invertebr Pathol. 2013 Jul;113(3):214-9. doi: 10.1016/j.jip.2013.03.010. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1016/j.jip.2013.03.010](http://1016/j.jip.2013.03.010)

**AUTORES / AUTHORS:** - Diaz S; Villalba A; Insua A; Soudant P; Fernandez-Tajes J; Mendez J; Carballal MJ

**INSTITUCIÓN / INSTITUTION:** - Centro de Investigacions Marinas, Xunta de Galicia, Apto. 13, 36620 Vilanova de Arousa, España.

**RESUMEN / SUMMARY:** - A proliferative disease, usually referred as disseminated neoplasia (DN), shows high prevalence in some cockle *Cerastoderma edule* beds of Galicia (NW España). Chromosome counts, examination of chromosome morphology, DNA quantification by flow cytometry and estimation of apoptosis frequency by TUNEL assay and flow cytometry were performed in cockles with different DN severity. Metaphases obtained from gills of DN-affected cockles displayed a chromosome number ranging from 41 to 145,

while normal number is 38; changes in chromosome morphology were also evident, with numerous microchromosomes occurring. Haemolymph flow cytometry analysis revealed difference in DNA content between healthy and DN-affected cockles. Aneuploid peaks ranged from 1.3n to 8.9n. Apoptosis frequency was determined on histological sections (TUNEL assay) and haemolymph samples (flow cytometry). Both techniques revealed neoplastic cells in apoptosis. The higher DN severity, the lower the percentage of apoptotic cells. According to flow cytometry results, the negative association between DN severity and apoptosis frequency only affected the neoplastic cells, whereas DN did not significantly affect the percentage of apoptotic hyalinocytes or apoptotic granulocytes.

[691]

**TÍTULO / TITLE:** - Anticancer activity of tolfenamic acid in medulloblastoma: a preclinical study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tumour Biol. 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s13277-013-0836-](#)

[6](#)

**AUTORES / AUTHORS:** - Eslin D; Lee C; Sankpal UT; Maliakal P; Sutphin RM; Abraham L; Basha R

**INSTITUCIÓN / INSTITUTION:** - MD Anderson Cancer Center Orlando, Orlando, FL, 32806, USA, [don.eslin@orlandohealth.com](mailto:don.eslin@orlandohealth.com).

**RESUMEN / SUMMARY:** - Medulloblastoma (MB) is the most common malignancy in children arising in the brain. Morbidities associated with intensive therapy are serious concerns in treating MB. Our aim was to identify novel targets and agents with less toxicity for treating MB. Specificity protein 1 (Sp1) transcription factor regulates several genes involved in cell proliferation and cell survival including survivin, an inhibitor of apoptosis protein. We previously showed that tolfenamic acid (TA), a nonsteroidal anti-inflammatory drug, inhibits neuroblastoma cell growth by targeting Sp1. We investigated the anticancer activity of TA using human MB cell lines and a mouse xenograft model. DAOY and D283 cells were treated with vehicle (dimethyl sulfoxide) or TA (5-50 µg/ml), and cell viability was measured at 1-3 days posttreatment. TA inhibited MB cell growth in a time- and dose-dependent manner. MB cells were treated with vehicle or TA (10 µg/ml), and the effect on cell apoptosis was measured. Apoptosis was analyzed by flow cytometry (annexin V staining), and caspase 3/7 activity was determined using Caspase-Glo kit. The expression of Sp1, cleaved poly(ADP-ribose) polymerase (c-PARP), and survivin was determined by Western blot analysis. TA inhibited the expression of Sp1 and survivin and upregulated c-PARP. Athymic nude mice were subcutaneously injected with D283 cells and treated with TA (50 mg/kg, three times per week) for 4 weeks. TA caused a decrease of ~40 % in tumor weight and volume. The tumor growth

inhibition was accompanied by a decrease in Sp1 and survivin expression in tumor tissue. These preclinical data demonstrate that TA acts as an anticancer agent in MB potentially targeting Sp1 and survivin.

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[692]

**TÍTULO / TITLE:** - Effects of Huaier aqueous extract on proliferation and apoptosis in the melanoma cell line A875.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Histochem. 2013 Apr 16. pii: S0065-1281(13)00031-7. doi: 10.1016/j.acthis.2013.02.010.

●●Enlace al texto completo (gratis o de pago)

[1016/j.acthis.2013.02.010](#)

**AUTORES / AUTHORS:** - Zhang F; Zhang Z; Liu Z

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, The First Affiliated Hospital of Harbin Medical University, Harbin, China.

**RESUMEN / SUMMARY:** - In recent years, an aqueous extract of the fungus *Trametes robiniophila* Murriell 1907 (Huaier) has been commonly used in China for complementary cancer therapy. However, the mechanisms of its anticancer effects are largely unknown. In the present study, we aimed to investigate the effects of Huaier extract on the inhibition of proliferation and promotion of apoptosis in a melanoma cell line, A875, and to explore the possible mechanisms of its anticancer effects. Cell proliferation was measured using a Cell Counting Kit-8 (CCK8) and PCNA-Western blot. The cell cycle distribution, and apoptosis levels were analyzed by flow cytometry, and Western blot was used to test the apoptotic pathways. We found that Huaier extract strongly inhibited cell proliferation of the A875 melanoma cells and induced G2/M arrest and apoptosis in a time- and dose-dependent manner. P53 expression was increased and cell apoptosis executed by caspase-3. Down-regulation of Bcl-2 and up-regulation of Bcl2-associated X protein (BAX) indicated that Huaier extract induced apoptosis through the mitochondrial pathway. As expected, the inhibitor Huaier decreased melanoma cell line A875 proliferation, and induced apoptosis in a time- and dose-dependent manner. Our findings indicate that Huaier extract is an effective complementary agent for cancer treatment of melanoma.

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[693]

**TÍTULO / TITLE:** - Butein and its emerging anti-proliferative and pro-apoptotic effects in systemic malignancies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Eye Res. 2013 Jul;38(7):810. doi: 10.3109/02713683.2013.785571. Epub 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago)

[3109/02713683.2013.785571](https://doi.org/10.1097/MIB.0b013e318280b169)

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**INSTITUCIÓN / INSTITUTION:** - 2400 Cary Street, Mechanicsville, VA , USA.

[694]

**TÍTULO / TITLE:** - The Cytotoxic Effects of Certolizumab Pegol and Golimumab Mediated by Transmembrane Tumor Necrosis Factor alpha.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Inflamm Bowel Dis. 2013 May;19(6):1224-31. doi: 10.1097/MIB.0b013e318280b169.

●●Enlace al texto completo (gratis o de pago)

[1097/MIB.0b013e318280b169](https://doi.org/10.1097/MIB.0b013e318280b169)

**AUTORES / AUTHORS:** - Ueda N; Tsukamoto H; Mitoma H; Ayano M; Tanaka A; Ohta S; Inoue Y; Arinobu Y; Niino H; Akashi K; Horiuchi T

**INSTITUCIÓN / INSTITUTION:** - \*Department of Medicine and Biosystemic Science, Kyushu University, Graduate School of Medical Sciences, Fukuoka, Japan daggerDepartment of Internal Medicine, Saga University, Saga, Japan double daggerResearch Fellow of the Japan Society for the Promotion of Science, Tokyo, Japan section signCenter for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: : Anti-tumor necrosis factor alpha (anti-TNF-alpha) agents have been successfully applied for the treatment of rheumatoid arthritis, Crohn's disease, and other chronic inflammatory diseases. Not only the neutralization of soluble TNF-alpha but also the effect on transmembrane TNF-alpha is important mechanisms of action of anti-TNF-alpha agents. This study investigated the cytotoxic effects of new anti-TNF-alpha agents, certolizumab pegol and golimumab, which are mediated by transmembrane TNF-alpha. METHODS: : Transmembrane TNF-alpha-expressing Jurkat T cells that did not express TNF receptors were used. The binding ability of each anti-TNF-alpha agent to transmembrane TNF-alpha, antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and the apoptotic effect were examined. RESULTS: : Certolizumab pegol and golimumab bound to transmembrane TNF-alpha. Golimumab induced antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, which was comparable to infliximab and adalimumab. However, certolizumab pegol did not induce antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity. Certolizumab pegol directly induced nonapoptotic cell death in transmembrane TNF-alpha-expressing cells. Golimumab induced a weaker apoptotic effect than infliximab and adalimumab. CONCLUSIONS: : The cytotoxic effects of anti-TNF-alpha agents on TNF-alpha-expressing cells are considered to be associated with the clinical effect of these agents on granulomatous diseases. The direct cytotoxic effect of

certolizumab pegol on TNF-alpha-producing cells may contribute to its clinical efficacy in Crohn's disease. Golimumab may be less effective for granulomatous diseases.

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[695]

**TÍTULO / TITLE:** - The Indole-3-carbinol Cyclic Tetrameric Derivative CTet Synergizes with Cisplatin and Doxorubicin in Triple-negative Breast Cancer Cell Lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Res. 2013 May;33(5):1867-72.

**AUTORES / AUTHORS:** - DE Santi M; Galluzzi L; Duranti A; Magnani M; Brandi G

**INSTITUCIÓN / INSTITUTION:** - Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Via Saffi 2, 61029 Urbino (PU), Italy.

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**RESUMEN / SUMMARY:** - Background/Aim: The indole-3-carbinol cyclic tetrameric derivative (CTet) inhibits breast cancer cell proliferation by endoplasmic reticulum stress and autophagy-related cell death induction, AKT/PKB (protein kinase B) activity inhibition and p53-independent overexpression of cyclin-dependent kinase inhibitor-1A (p21/CDKN1A). In the present study we evaluated the synergistic activity of CTet in combination with cisplatin and doxorubicin in triple-negative breast cancer cell lines. MATERIALS AND METHODS: Synergisms were evaluated in terms of cell viability, induction of autophagy and overexpression of microtubule-associated protein-1 light chain-3 beta (MAP1LC3B) autophagy-related gene in MDA-MB-231 and BT-20 triple-negative breast cancer cells. RESULTS: We demonstrated that CTet in combination with both cisplatin and doxorubicin synergistically inhibits cell viability and induces autophagy. The MAP1LC3B gene was synergistically overexpressed in MDA-MB-231 cells treated with CTet-cisplatin combination. Moreover, the cytotoxic activity of CTet was improved in cells pre-treated with cisplatin and doxorubicin. CONCLUSION: This preliminary in vitro study confirms the potential of CTet as a chemopreventive agent or chemotherapeutic in combination with standard approaches for triple-negative breast cancer.

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[696]

**TÍTULO / TITLE:** - RNA interference targeting adrenomedullin induces apoptosis and reduces the growth of human bladder urothelial cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Oncol. 2013 Sep;30(3):616. doi: 10.1007/s12032-013-0616-6. Epub 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s12032-013-0616-](#)

[6](#)

**AUTORES / AUTHORS:** - Liu AG; Zhang XZ; Li FB; Zhao YL; Guo YC; Yang RM

**INSTITUCIÓN / INSTITUTION:** - Department of Interventional Therapy, The First Affiliated Hospital of Xinxiang Medical University, Weihui, China.

**RESUMEN / SUMMARY:** - Adrenomedullin (ADM) is a potent, long-lasting angiogenic peptide that was originally isolated from human pheochromocytoma. ADM signaling is of particular significance in endothelial cell biology because the peptide protects cells from apoptosis, and ADM has been shown to be pro-tumorigenic in that it stimulates tumor cell growth and angiogenesis. ADM may be involved in micro-vessel proliferation and partially in the release of hypoxia in solid tumors, contributing to the proliferation of tumor cells as well as local tumor invasion and metastasis. However, the effect of hypoxia-induced ADM expression in bladder cancer remains unclear. Here, we found that the levels of ADM protein in tumor tissue from patients with bladder urothelial cell carcinoma were significantly increased compared to the adjacent non-tumor bladder tissues ( $p < 0.01$ ). Under hypoxic conditions, the expression of ADM was significantly elevated in a time-dependent manner in human bladder cancer cell lines. Furthermore, the knockdown of ADM by shRNA in T24 cells showed obvious apoptosis compared to untransfected controls ( $p < 0.0001$ ). In addition, the combination of cisplatin and ADM-shRNA significantly reduces the tumor growth in vivo compared to treatment with cisplatin ( $p = 0.0046$ ) or ADM-shRNA alone ( $p < 0.0001$ ). These data suggest that ADM plays an important role in promoting bladder cancer cell growth under hypoxia and that the inhibition of ADM may provide a target for bladder cancer therapy.

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[697]

**TÍTULO / TITLE:** - Evaluation of the Retinoids With Cisplatin and Vincristine in Xenograft Models of Neuroblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pediatr Hematol Oncol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago)

[1097/MPH.0b013e3182915d4a](#)

**AUTORES / AUTHORS:** - Norris RE; Nguyen VT; Adamson PC

**INSTITUCIÓN / INSTITUTION:** - \*Division of Pediatric Hematology/Oncology, Rainbow Babies and Children's Hospital, Cleveland, OH daggerDivision of Clinical Pharmacology & Therapeutics, Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA.

**RESUMEN / SUMMARY:** - Retinoids have been studied for the treatment of children with neuroblastoma for >25 years. Posttransplant administration of isotretinoin is standard of care for children with high-risk neuroblastoma, whereas fenretinide remains investigational. Previous preclinical studies have evaluated the interaction of retinoids and cytotoxic agents with conflicting results. We evaluated the schedule-dependent interaction of the cytotoxic agents, vincristine and cisplatin, with the retinoids, isotretinoin and fenretinide, in xenograft models of neuroblastoma. Concomitant administration of

isotretinoin or fenretinide with the cytotoxic agents did not result in any clear potentiation of cytotoxicity.

[698]

**TÍTULO / TITLE:** - Dual inhibitor of phosphoinositide 3-kinase/mammalian target of rapamycin NVP-BEZ235 effectively inhibits cisplatin-resistant urothelial cancer cell growth through autophagic flux.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Toxicol Lett. 2013 May 4. pii: S0378-4274(13)00176-8. doi: 10.1016/j.toxlet.2013.04.021.

●●Enlace al texto completo (gratis o de pago)

[1016/j.toxlet.2013.04.021](http://1016/j.toxlet.2013.04.021)

**AUTORES / AUTHORS:** - Li JR; Cheng CL; Yang CR; Ou YC; Wu MJ; Ko JL

**INSTITUCIÓN / INSTITUTION:** - Institute of Medicine, Chung Shan Medical University, Taiwan; Division of Urology, Department of Surgery, Taichung Veterans General Hospital, Taiwan; Institute of Medical and Molecular Toxicology, Chung Shan Medical University, Taiwan.

**RESUMEN / SUMMARY:** - PURPOSE: Therapeutically induced autophagic cell death has been proven to be effective in cases of solid tumors. The dual phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitor NVP-BEZ235 possesses antitumor activity against solid tumors. Inhibition of mTOR has been shown to elicit autophagy. In this study, we examined the antiproliferation and autophagic activities of NVP-BEZ235 in parental and cisplatin-resistant urothelial carcinoma (UC) cells. MATERIALS AND METHODS: Two UC cell lines, NTUB1 and a cisplatin-resistant subline N/P(14), were applied to examine the cytotoxic effect of NVP-BEZ-235. The cell death mechanism was also evaluated. RESULTS: NVP-BEZ235 was effective in inhibiting the growth of UC cells including parental and cisplatin-resistant cells on flow cytometry assay and Western blot. Although NVP-BEZ235 did not induce LC3-II conversion, it did elicit acidic vesicular organelle (AVO) development on flow cytometry. On Western blot, NVP-BEZ235 decreased p62 and phospho-Rb expressions in a concentration-dependent manner. GFP-LC3 conversion and the appearance of cleaved-GFP following NVP-BEZ235 treatment were demonstrated on Western blot. In addition, lysosomotropic inhibition of autophagy by chloroquine (CQ), an agent that is currently in clinical use and a known antagonist of autophagy, resulted in proliferation of UC cells. Thus, inhibition of autophagic flux by CQ appears to be a survival mechanism that counteracts the anticancer effects of NVP-BEZ235. CONCLUSIONS: We demonstrated that NVP-BEZ235 inhibits UC cell proliferation by activating autophagic flux and cell cycle arrest, but does not induce apoptotic cell death. Our findings suggest that the anticancer efficacy of NVP-BEZ235 is due to autophagic flux and co-treatment with CQ counteracts the cytotoxic effect.

[699]

**TÍTULO / TITLE:** - Identification of two new HLA-A\*0201-restricted cytotoxic T lymphocyte epitopes from colorectal carcinoma-associated antigen PLAC1/CP1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gastroenterol. 2013 Apr 21.

●●Enlace al texto completo (gratis o de pago) [1007/s00535-013-0811-4](#)

**AUTORES / AUTHORS:** - Liu F; Zhang H; Shen D; Wang S; Ye Y; Chen H; Pang X; Song Q; He P

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Peking University People's Hospital, Beijing, 100044, People's Republic of China, [liufangfang@pkuph.edu.cn](mailto:liufangfang@pkuph.edu.cn).

**RESUMEN / SUMMARY:** - BACKGROUND: To explore the potential application of placenta-specific PLAC1/Cancer Placenta (CP) 1 antigen for immunotherapy in CRC patients, further identification of the cytotoxic T lymphocyte epitopes from this antigen is necessary. METHODS: We assessed the protein expression of PLAC1/CP1 using a tissue chip and immunohistochemistry staining in CRC samples. Simultaneously, we predicted four PLAC1/CP1-derived HLA-A\*0201-restricted peptides by using reverse immunology methods. Peptide-specific CD8+ T cell responses were assessed by an IFN-gamma release ELISPOT assay. Effector CD8+ T cells lyse HLA-A\*0201 CRC cell line SW620 was detected in a granzyme-B release ELISPOT cytotoxicity assay. RESULTS: Our results indicated that PLAC1/CP1 was highly expressed in 56.7 % (55/97) of adenocarcinomas. PLAC1/CP1 protein expression was associated with CRC tumor differentiation, the tumor/node/metastasis stage, and lymph node metastasis. Two of four peptides showed high affinities in an HLA-A2 binding assay. In 66.7 % (6/9) of peripheral blood mononuclear cells of CRC samples with PLAC1/CP1 protein-positive expression, these two peptides, PLAC1/CP1 p41-50 (FMLNNDVCV) and PLAC1/CP1 p69-77 (HAYQFTYRV), were immunogenic in the induction of peptide-specific CD8+ T cell responses as assessed by an IFN-gamma release ELISPOT assay. Furthermore, the generated effector CD8+ T cells could specifically lyse the PLAC1/CP1 HLA-A\*0201 CRC cell line SW620 in a granzyme-B release ELISPOT cytotoxicity assay. CONCLUSIONS: These results show that the PLAC1/CP1 antigen is a possible prognostic marker of CRC and that PLAC1/CP1 p41-50 and PLAC1/CP1 p69-77 are novel HLA-A\*0201-restricted CD8+ T cell epitopes and potential targets for peptide-based immunotherapy in CRC patients.

[700]

**TÍTULO / TITLE:** - Bortezomib inhibits proteasomal degradation of I kappa B alpha and induces Mitochondrial dependent Apoptosis in Activated B-Cell Diffuse Large B-Cell Lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 May 23.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.806799](https://doi.org/10.3109/10428194.2013.806799)

**AUTORES / AUTHORS:** - Bu R; Hussain AR; Al-Obaisi KA; Ahmed M; Uddin S; Al-Kuraya KS

**RESUMEN / SUMMARY:** - Activated B-cell lymphoma (ABC), a subgroup of Diffuse Large B-cell lymphoma (DLBCL) has a worse survival after upfront chemotherapy and is characterized by constitutive activation of the anti-apoptotic nuclear factor-kappa B (NFkappaB) pathway. Implication of NFkappaB inhibition in ABC has not yet been fully explored as a potential therapeutic target. Therefore, a panel of ABC cell lines was used to examine the effect of Bortezomib, a proteasome inhibitor which blocks degradation of I kappa B alpha and consequently inhibits NFkappaB activity. Our data showed that Bortezomib caused a dose-dependent growth inhibition and induction of apoptosis in all cell lines studied. We next determined the status of NFkappaB pathway following Bortezomib treatment and found that there was accumulation of I kappa B alpha without affecting its phosphorylation status at early time point. Electrophoretic mobility shift assay showed that Bortezomib treatment inhibited constitutive nuclear NFkappaB in ABC cell lines. Furthermore, treatment of ABC cell lines with Bortezomib for 48 hours also down-regulated expression of NFkappaB-regulated gene products, such as I kappa B alpha, Bcl-2, Bcl-XL, XIAP and Survivin leading to apoptosis via the mitochondrial apoptotic pathway. Altogether, these results suggest that NFkB may be a potential target for therapeutic intervention in DLBCL using proteasomal inhibitors such as Bortezomib.

[701]

**TÍTULO / TITLE:** - A two-dimensional model for studying tumor angiogenesis inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Invest. 2013 Jun;31(5):346-58. doi: 10.3109/07357907.2013.789902. Epub 2013 May 3.

●●Enlace al texto completo (gratis o de pago)

[3109/07357907.2013.789902](https://doi.org/10.3109/07357907.2013.789902)

**AUTORES / AUTHORS:** - Gao P; Yang JL; Wang H; Wu XD; Jiao SC

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, General Hospital of Chinese PLA, Beijing, China.

**RESUMEN / SUMMARY:** - Inhibition of angiogenesis can attenuate tumor growth. Hence, mathematical modeling of tumor-induced angiogenesis can be a tool for

predicting outcome of angiogenesis inhibitors. We have generated a two-dimensional cornea model of angiogenesis and have tested the effectiveness of the inhibitor through testing representative examples. The effects of thrombospondin and the way it interacts in the cornea with the endothelial cells and tumor angiogenic factors were examined. We were then able to define the inhibitor's role specific to our benchmark model. Finally, a thorough sensitivity analysis was performed to verify baseline values and determine the precise effects of the different parameters. Our findings can be used to design strategies involving manufacturing inhibitors to regulate the angiogenesis process.

[702]

**TÍTULO / TITLE:** - MAPK inhibitors augment gallic acid-induced A549 lung cancer cell death through the enhancement of glutathione depletion.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Jul;30(1):513-9. doi: 10.3892/or.2013.2447. Epub 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [3892/or.2013.2447](#)

**AUTORES / AUTHORS:** - Park WH; Kim SH

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju 561-180, Republic of Korea.

**RESUMEN / SUMMARY:** - Gallic acid (GA) is involved in various biological processes such as cell growth inhibition and apoptosis through changes in reactive oxygen species (ROS). In the present study, we investigated the effects of MAPK (MEK, JNK or p38) inhibitors on cell death in GA-induced A549 lung cancer cells in relation to ROS and glutathione (GSH). Treatment with 100 microM GA inhibited the growth of A549 cells and induced apoptosis and/or necrosis, which was accompanied by the loss of mitochondrial membrane potential (MMP;  $\Psi_{\text{m}}$ ). GA increased ROS levels as well as GSH depletion in A549 cells at 24 h. MEK inhibitor seemed to enhance cell growth inhibition by GA. This inhibitor also increased cell death, MMP ( $\Psi_{\text{m}}$ ) loss and GSH depletion in GA-treated A549 cells. Both JNK and p38 inhibitors intensified growth inhibition, cell death, MMP ( $\Psi_{\text{m}}$ ) loss and GSH depletion by GA. However, none of the MAPK inhibitors significantly altered ROS levels in GA-treated A549 cells. In conclusion, MAPK inhibitors enhanced growth inhibition and death in GA-treated A549 cells, which were correlated with GSH depletion rather than ROS levels.

[703]

**TÍTULO / TITLE:** - Modulating the cyclic guanosine monophosphate substrate selectivity of the phosphodiesterase 3 inhibitors by pyridine, pyrido[2,3-

d]pyrimidine derivatives and their effects upon the growth of HT-29 cancer cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chem Pharm Bull (Tokyo). 2013;61(4):405-10.

**AUTORES / AUTHORS:** - Abadi AH; Hany MS; Elsharif SA; Eissa AA; Gary BD; Tinsley HN; Piazza GA

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Biotechnology, German University in Cairo, Egypt.

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**RESUMEN / SUMMARY:** - Analogues with the scaffolds of 3-cyano-4-alkoxyphenyl-6-bromoaryl-2-pyridone and 2-amino-3-cyano-4-alkoxyphenyl-6-bromoarylpyridine were synthesized. Cyclization of the 2-amino derivatives with formic acid and formamide gave the corresponding pyrido[2,3-d]pyrimidin-4(3H)-one and the pyrido[2,3-d]-pyrimidin-4-amine derivatives, respectively. Active phosphodiesterase 3 (PDE3) inhibitors were identified from each of the four aforementioned scaffolds. This is the first report that pyrido[2,3-d]pyrimidin-4(3H)-one and pyrido[2,3-d]pyrimidin-4-amine derivatives can inhibit PDE3. The analogues with the pyridone and pyrido[2,3-d]pyrimidin-4(3H)-one scaffolds inhibited both cAMP and cyclic guanosine monophosphate (cGMP) hydrolysis by PDE3, while the amine containing scaffolds were more selective for cGMP hydrolysis. This observation may set the base for substrate-selective pharmacological modulation of this important class of drug targets and with less side effects, particularly tachycardia. The dual inhibitors of PDE3 were more potent inhibitor towards the growth of HT-29 cancer cell lines.

[704]

**TÍTULO / TITLE:** - O-methylguanine-DNA methyltransferase (MGMT) immunohistochemistry as a predictor of resistance to temozolomide in primary CNS lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Neurooncol. 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s11060-013-1162-y](http://1007/s11060-013-1162-y)

**AUTORES / AUTHORS:** - Jiang X; Reardon DA; Desjardins A; Vredenburgh JJ; Quinn JA; Austin AD; Herndon JE 2<sup>nd</sup>; McLendon RE; Friedman HS

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Duke University Medical Center, Box 3712 DUMC, Durham, NC, 27710, USA, [jiang009@mc.duke.edu](mailto:jiang009@mc.duke.edu).

**RESUMEN / SUMMARY:** - Temozolomide, an alkylating agent, has shown promise in treating primary central nervous system lymphoma (PCNSL). The enzyme O6-methylguanine-DNA methyltransferase (MGMT) repairs alkylating damage, such as that induced by temozolomide. We hypothesized that MGMT immunohistochemistry would predict resistance to temozolomide in PCNSL. A retrospective study of newly-diagnosed and recurrent PCNSL patients treated at

our institution was conducted to study the predictive value of MGMT immunohistochemistry for response to temozolomide. 20 patients who were treated with temozolomide as a single agent were identified during the study time period. 6/20 patients demonstrated a response, corresponding to an objective response rate of 30 % (95 % CI 8-52). Five patients with low MGMT level (<30 %) showed a response to temozolomide. Only one of 10 patients (10 %) with high MGMT level ( $\geq$ 30 %) exhibited a response to temozolomide. Small sample numbers precluded formal statistical comparisons. Two patients with complete response remain alive without progressive disease 6.7 and 7.2 years after temozolomide initiation. Immunohistochemistry can be performed on small biopsies to selectively assess MGMT status in tumor versus surrounding inflammation. MGMT analysis by immunohistochemistry may predict response to temozolomide in PCNSL and should be prospectively investigated.

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[705]

**TÍTULO / TITLE:** - The inhibin-betaC subunit is down-regulated, while inhibin-betaE is up-regulated by interferon-beta1a in Ishikawa carcinoma cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Gynecol Obstet. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1007/s00404-013-2848-](http://1007/s00404-013-2848-2)

[2](#)

**AUTORES / AUTHORS:** - Juckstock J; Kimmich T; Mylonas I; Friese K; Dian D

**INSTITUCIÓN / INSTITUTION:** - 1<sup>st</sup> Department of Obstetrics and Gynaecology, Ludwig-Maximilians-University Munich, Maistrasse 11, 80337, Munich, Germany.

**RESUMEN / SUMMARY:** - INTRODUCTION: Inhibins are important regulators of the female reproductive system. Recently, two new inhibin-subunits betaC and betaE have been described, although, their function is still quite unclear. Interestingly, there is an association between interferon and TGF-beta expression. Therefore, the aim of this study was to determine expression changes of inhibin-betaC and -betaE subunits in endometrial Ishikawa carcinoma cell line after stimulation with interferon-beta1a. MATERIALS AND METHODS: The Ishikawa cell line was cultured until confluence was observed (after 2 days). After adding interferon-beta1a (1,000 IE/ml), Ishikawa cells were analyzed for inhibin-betaC and -betaE subunits by RT-PCR. The fibroblast cell line BJ6 served as negative control. Experiments were performed in triplicates. RESULTS: The endometrial adenocarcinoma cell line Ishikawa synthesized the inhibin- betaC and -betaE subunits. The fibroblast cells BJ6 did not demonstrate an inhibin -betaC and -betaE mRNA expression, while inhibin-betaC subunit is down-regulated and inhibin-betaE is up-regulated in Ishikawa carcinoma cell line after stimulation with interferon-beta1a in Ishikawa. DISCUSSION: We demonstrated for the first time a functional relationship between interferon and the novel inhibin-betaC and -betaE subunits. It might be possible that interferon

exerts a possible apoptotic function through the betaE-subunit, while, by down-regulating the betaC isoform, cell proliferation is inhibited. However, the precise function of the novel betaC- and betaE-subunits are still not known in human endometrial tissue and a possible association with interferon is still unclear and warrants further research.

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[706]

**TÍTULO / TITLE:** - Anti-cancer effect of a quinoxaline derivative GK13 as a transglutaminase 2 inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 Apr 21.

●●Enlace al texto completo (gratis o de pago) [1007/s00432-013-1433-](http://1007/s00432-013-1433-1)

[1](#)

**AUTORES / AUTHORS:** - Lee SH; Kim N; Kim SJ; Song J; Gong YD; Kim SY

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Yonsei University, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - PURPOSE: Transglutaminase 2 (TGase 2), a cross-linking enzyme, plays an important role in both pro-survival and anti-apoptosis during oncogenesis. For instance, TGase 2 induces NF-kappaB activation through I-kappaBalpha polymerization, which leads to the increase of pro-survival factors such as BCL-2. TGase 2 also suppresses apoptosis via depletion of caspase 3 and cathepsin D. Therefore, a specific TGase 2 inhibitor may become a very useful treatment for cancer showing high levels of TGase 2 expression. METHODS: By small-molecule library screening, we managed to locate a competitive TGase 2 inhibiting quinoxaline compound (GK13) from 50 other quinoxaline derivatives. The 50 compounds that were screened represent a thousand structurally diverse, potentially pharmaceutical heterocyclic compound libraries, including benzopyrans, oxadiazoles, thiadiazoles, and quinoxalines. By measuring GI50, TGI, and LC50 using SRB assay, GK13 was selected. RESULTS: In vitro enzyme kinetics using guinea pig liver TGase 2 showed that IC50 value was about 16.4 E-6 M. GK13 inhibits TGase 2-mediated I-kappaBalpha polymerization in a dose-dependent manner. LC50 of GK13 showed greater efficacy as 4.3E-4 M than LC50 of doxorubicin that showed efficacy as 3.87E-3 M in NCC72 composing 11 tissue origins and 72 cancer cell lines. CONCLUSION: GK13 showed a possibility that quinoxaline derivatives may be effective for anti-cancer activity via TGase 2 inhibition.

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[707]

**TÍTULO / TITLE:** - The apoptosis of non-small cell lung cancer induced by cisplatin through modulation of STIM1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Toxicol Pathol. 2013 May 25. pii: S0940-2993(13)00055-9. doi: 10.1016/j.etp.2013.04.003.

●●Enlace al texto completo (gratis o de pago) [1016/j.etp.2013.04.003](http://1016/j.etp.2013.04.003)

**AUTORES / AUTHORS:** - Li W; Zhang M; Xu L; Lin D; Cai S; Zou F

**INSTITUCIÓN / INSTITUTION:** - Department of Occupational Health and Occupational Medicine, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou, Guangdong Province 510515, China.

**RESUMEN / SUMMARY:** - Cis-diamminedichloroplatinum (II) (cisplatin) is one of the most active antitumor agents used in human chemotherapy of non-small cell lung cancer. Cisplatin forms crosslinked DNA adducts and its cytotoxicity has been shown to be mediated by propagation of DNA damage recognition signals to downstream pathways prompting apoptosis. The steps involved in the process include changes in Ca<sup>2+</sup> signaling with dysregulated tumor cell turnover. Stromal interaction molecules 1 (STIM1), as one of the most potent tumor suppressor genes, are identified as the endoplasmic-reticulum (ER) Ca<sup>2+</sup> sensor controlling store-operated Ca<sup>2+</sup> entry (SOCE) in non-excitable cells, which is main pathway to extracellular Ca<sup>2+</sup> influx. Its role in STIM1 cisplatin-induced apoptosis of non-small cell lung cancer was the focus of study with focus on SOCE inhibitors 2-APB- and SKF96365-cisplatin-induced apoptosis in the non-small cell lung cancer (NSCLC) cell lines A549 and H460. In this experimental model, cisplatin-induced apoptosis and decreased concentration of intracellular Ca<sup>2+</sup> was demonstrated. The expression of STIM1 was significantly higher in carcinoma tissue than in the adjacent non-neoplastic lung tissue. These findings support the conclusion that STIM1 may play an important role in the development of NSCLC which makes drugs that repress the expression of STIM1 to be a potential target for lung cancer therapy.

[708]

**TÍTULO / TITLE:** - Trans-resveratrol loaded chitosan nanoparticles modified with biotin and avidin to target hepatic carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Pharm. 2013 May 16. pii: S0378-5173(13)00406-7. doi: 10.1016/j.ijpharm.2013.05.007.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ijpharm.2013.05.007](http://1016/j.ijpharm.2013.05.007)

**AUTORES / AUTHORS:** - Bu L; Gan LC; Guo XQ; Chen FZ; Song Q; Qi-Zhao; Gou XJ; Hou SX; Yao Q

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Sichuan Province of Medicinal Chemistry, Chengdu University, Chengdu 610106, PR China; Department of Endocrinology, Shanghai 10<sup>th</sup> People's Hospital, Tongji University School of Medicine, 301 Yanchang Road, Shanghai 200072, PR China.

**RESUMEN / SUMMARY:** - Conventional liver targeted system focuses on delivering drugs to liver, bringing toxicity on hepatic normal tissues. The

purpose of this study is to construct a new system capable of specially targeting to hepatic carcinoma instead of the whole liver. Based on the fact that nanoparticles (NPs) bound with either biotin or avidin tend to accumulate in tumors and avidin-attached reagents were quickly eliminated from blood circulation and assembled in liver, trans-resveratrol loaded chitosan nanoparticles (CS-NPs), CS-NPs with the surface modified either by biotin (B-CS-NPs) or by both biotin and avidin (A-B-CS-NPs) were prepared and their physiochemical properties were investigated. The in vitro release profiles of the three NPs all conformed to bioexponential equation. Pharmacokinetic experiment indicated that A-B-CS-NPs rapidly assembled in liver after injection, with the highest liver targeting index of 2.70, while the modification of biotin attenuated the liver targeting ability of NPs. Inhibitory study on HepG2 cells declared that compared to trans-resveratrol solution and CS-NPs, both B-CS-NPs and A-B-CS-NPs significantly improved the anticancer activity. When incubated with HepG2 cells at high concentration for longer time, A-B-CS-NPs exhibited superior cytotoxicity than B-CS-NPs. This study exclaims that A-B-CS-NPs may be a potent drug delivery vector specially targeting to hepatic carcinoma.

[709]

**TÍTULO / TITLE:** - Erratum to: Prediction of Drug-Drug Interactions Between Various Antidepressants and Efavirenz or Boosted Protease Inhibitors Using a Physiologically Based Pharmacokinetic Modelling Approach.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Pharmacokinet. 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1007/s40262-013-0066-](#)

[5](#)

**AUTORES / AUTHORS:** - Siccardi M; Marzolini C; Seden K; Almond L; Kirov A; Khoo S; Owen A; Back D

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, 70 Pembroke Place, Liverpool, L69 3GF, UK, [siccardi@liverpool.ac.uk](mailto:siccardi@liverpool.ac.uk).

[710]

**TÍTULO / TITLE:** - Downregulation of chromatin remodeling factor CHD5 is associated with a poor prognosis in human glioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Clin Neurosci. 2013 May 23. pii: S0967-5868(12)00589-9. doi: 10.1016/j.jocn.2012.07.021.

●●Enlace al texto completo (gratis o de pago) [1016/j.jocn.2012.07.021](#)

**AUTORES / AUTHORS:** - Wang L; He S; Tu Y; Ji P; Zong J; Zhang J; Feng F; Zhao J; Gao G; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Tangdu Hospital, No. 569, Xinsi Road, Baqiao District, Xi'an City 710038, China.

**RESUMEN / SUMMARY:** - Chromodomain helicase DNA-binding protein 5 (CHD5), a member of the CHD family, is involved in key cellular processes including chromatin remodeling, cell cycle regulation, and cellular adhesion. Recent studies have demonstrated that CHD5 is the product of a novel tumor suppressor gene and is implicated in certain tumor types. However, the clinicopathological significance of CHD5 expression in human malignant gliomas remains unclear. To address this problem, CHD5 expression in human gliomas and non-neoplastic brain tissues was measured using real-time quantitative polymerase chain reaction (RT-PCR) assay, Western blot, and immunohistochemistry. The association of CHD5 immunostaining with clinicopathological factors or prognosis of glioma patients was statistically analyzed. Genetic and protein expression of CHD5 were downregulated in glioma tissues compared to corresponding non-neoplastic brain tissues (both  $p < 0.001$ ). Additionally, decreased expression of CHD5 in glioma was significantly associated with pathological grade ( $p = 0.007$ ); high pathological grade was associated with low CHD5 expression. Loss of CHD5 protein expression was also significantly correlated with a low Karnofsky performance scale score ( $p = 0.01$ ). Moreover, overall survival of patients with low CHD5 protein expression was dramatically shorter than those of patients with high CHD5 protein expression ( $p = 0.003$ ). Multivariate Cox regression analysis indicated that CHD5 expression was an independent prognostic factor for patients with gliomas ( $p = 0.01$ ). In conclusion, these data offer convincing evidence for the first time that CHD5 might act as a tumor suppressor in glioma, may act as a regulator of aggressive development, and is a candidate prognostic marker for this malignancy.

[711]

**TÍTULO / TITLE:** - Phase II Trial of Erlotinib for Japanese Patients With Previously Treated Non-small-cell Lung Cancer Harboring EGFR Mutations: Results of Lung Oncology Group in Kyushu (LOGiK0803).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Jpn J Clin Oncol. 2013 Jun;43(6):629-35. doi: 10.1093/jjco/hyt056. Epub 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago) [1093/jjco/hyt056](#)

**AUTORES / AUTHORS:** - Yamada K; Takayama K; Kawakami S; Saruwatari K; Morinaga R; Harada T; Aragane N; Nagata S; Kishimoto J; Nakanishi Y; Ichinose Y

**INSTITUCIÓN / INSTITUTION:** - \*Division of Respiratory, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume City, Fukuoka 830-0011, Japan.

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**RESUMEN / SUMMARY:** - OBJECTIVE: Erlotinib has been reported to be useful for treatment of non-small-cell lung cancer harboring mutation of the epidermal growth factor receptor gene EGFR-mt. However, no prospective trial has yet assessed the utility of erlotinib in Japanese patients. METHODS: Patients with EGFR-mt (exon 19/21) non-small-cell lung cancer who had previously received one to two chemotherapy regimens were enrolled in this trial. Erlotinib was initially administered at a dose of 150 mg/day orally until disease progression or unacceptable toxicities occurred. The primary endpoint was the objective response rate. RESULTS: Twenty-six patients were enrolled between February 2009 and January 2011. Objective response was observed in 14 patients (53.8%, 95% confidence interval: 33.4-73.4%), and the disease control rate reached 80.8% (95% confidence interval: 60.7-93.5%). After a median follow-up time of 17.3 months (range: 5.8-29.5 months), the median progression-free survival was 9.3 months (95% confidence interval: 7.6-11.6 months). The median survival time is yet to be determined. Major toxicities were skin disorder and liver dysfunction; most episodes were grade 2 or less, and all were tolerable. Only one patient with grade 3 skin rash discontinued the study. No patients developed interstitial lung disease, and there were no treatment-related deaths. CONCLUSIONS: This prospective study is the first to have investigated the usefulness of erlotinib in Japanese patients with previously treated EGFR-mt non-small-cell lung cancer. Although this trial could not meet the primary endpoint, erlotinib was well tolerated and showed clinical benefit such as promising disease control rate or progression-free survival in this population, similar to gefitinib.

[712]

**TÍTULO / TITLE:** - Annexin A1: A new biomarker for predicting nasopharyngeal carcinoma response to radiotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Hypotheses. 2013 May 6. pii: S0306-9877(13)00189-8. doi: 10.1016/j.mehy.2013.04.019.

●●Enlace al texto completo (gratis o de pago)

[1016/j.mehy.2013.04.019](http://1016/j.mehy.2013.04.019)

**AUTORES / AUTHORS:** - Zeng GQ; Cheng AL; Tang J; Li GQ; Li MX; Qu JQ; Cao C; Liao L; Xiao ZQ

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University, Changsha 410008, China; School of Nursing, University of South China, Hengyang 421001, China.

**RESUMEN / SUMMARY:** - Radiotherapy is the primary treatment for nasopharyngeal carcinoma (NPC), but radioresistance remains a serious obstacle to successful treatment in many cases. Therefore, the biomarkers for predicting NPC response to radiotherapy are very important for targeted therapy

and individualized radiotherapy of NPC. Accumulating evidences have shown that Annexin A1 was correlated with NPC radioresistance. First, Annexin A1 is a potential tumor suppressor gene, and can regulate tumor cell proliferation and apoptosis, thus abnormal expression of Annexin A1 in NPC affects apoptosis of tumor cells induced by ionizing radiation and radiotherapeutic efficacy. Second, Annexin A1 is one of the proteins that are involved in p53-mediated radioresponse in NPC, and it might be related to NPC radioresistance. Third, the expression level of Annexin A1 is down-regulated in NPC, and is correlated with metastasis, recurrence and poor prognosis of NPC, thus Annexin A1 downregulation may increase NPC radioresistance, leading to poor prognosis. Last but not the least, Annexin A1 is closely related with tumor chemoresistance, whereas radioresistance is similar to chemoresistance in many aspects, thus Annexin A1 may also be involved in NPC radioresistance. Based on the above mentions, we hypothesize that Annexin A1 is closely correlated with NPC radioresistance and is an important new biomarker for predicting NPC response to radiotherapy.

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[713]

**TÍTULO / TITLE:** - FLT3 TYROSINE KINASE INHIBITORS IN ACUTE MYELOID LEUKEMIA: CLINICAL IMPLICATIONS AND LIMITATIONS.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.800198](#)

**AUTORES / AUTHORS:** - Kayser S; Levis MJ

**RESUMEN / SUMMARY:** - Abstract Internal tandem duplications of the FMS-like tyrosine kinase 3 (FLT3) gene are one of the most frequent gene mutations in acute myeloid leukemia (AML) and are associated with poor clinical outcome. The remission rate is high with intensive chemotherapy, but most of the patients eventually relapse. During the last decade, FLT3 mutations have emerged as an attractive target for a molecularly-specific treatment strategy. Targeting FLT3 receptor tyrosine kinases in AML has shown encouraging results in the treatment of FLT3 mutated AML, but in most of the patients responses are incomplete and not sustained. Newer, more specific compounds seem to have a higher potency and selectivity against FLT3. During therapy with FLT3 tyrosine kinase inhibitors (TKIs) the induction of acquired resistance has emerged as a clinical problem. Therefore, optimization of the targeted therapy and potential treatment options to overcome resistance is currently the focus of clinical research. In this review we discuss the use and limitations of TKIs as a therapeutic strategy for the treatment of FLT3 mutated AML, including mechanisms of resistance to TKIs as well as possible novel strategies to improve FLT3 inhibitor therapy.

[714]

**TÍTULO / TITLE:** - EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND INTRAVITREAL ANTI-VEGF THERAPY WITH BEVACIZUMAB IN VASOPROLIFERATIVE RETINAL TUMORS.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Retina. 2013 May 6.

●●Enlace al texto completo (gratis o de pago)

[1097/IAE.0b013e3182923490](#)

**AUTORES / AUTHORS:** - Saito W; Kase S; Fujiya A; Dong Z; Noda K; Ishida S

**INSTITUCIÓN / INSTITUTION:** - Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

**RESUMEN / SUMMARY:** - **PURPOSE::** To examine whether vasoproliferative retinal tumors (VPRTs) express vascular endothelial growth factor and respond to intravitreal bevacizumab injection. **METHODS::** Retrospective interventional case series. Intravitreal bevacizumab 1.25 mg was administered to 9 patients with VPRT-associated neovascularization or exudative retinal changes. The changes of the tumor size, best-corrected visual acuity, and central retinal thickness were evaluated before and after treatment. Immunohistochemistry with anti-vascular endothelial growth factor antibody in an excised tissue of VPRT during pars plana vitrectomy was performed. **RESULTS::** In two patients with small tumors (within two disk diameters), the tumors disappeared or regressed with only one injection of intravitreal bevacizumab injection. Larger tumors regressed after additional laser photocoagulation and/or cryotherapy without recurrence of exudative retinal changes in six eyes, although these did not regress by intravitreal bevacizumab injection alone. The mean logarithm of the minimal angle of resolution value of best-corrected visual acuity and central retinal thickness at the final visit were significantly improved compared with those of pretreatment ( $P = 0.02$  and  $P = 0.03$ , respectively). Immunoreactivity for vascular endothelial growth factor was strongly detected in the resected tumor tissue. **CONCLUSION::** These results suggest that vascular endothelial growth factor derived from VPRTs causes retinal neovascularization or exudative retinal changes associated with VPRTs. Intravitreal bevacizumab may be a useful therapeutic option for these complications secondary to VPRTs.

[715]

**TÍTULO / TITLE:** - INTERLEUKIN 8 PROMOTER POLYMORPHISM PREDICTS THE INITIAL RESPONSE TO BEVACIZUMAB TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Retina. 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago)

[1097/IAE.0b013e318285cf92](https://doi.org/10.1097/IAE.0b013e318285cf92)

**AUTORES / AUTHORS:** - Hautamaki A; Kivioja J; Vavuli S; Kakko S; Savolainen ER; Savolainen MJ; Liinamaa MJ; Seitsonen S; Onkamo P; Jarvela I; Immonen I

**INSTITUCIÓN / INSTITUTION:** - \*Department of Ophthalmology, Helsinki University Central Hospital, Helsinki, Finland daggerDepartment of Medical Genetics, University of Helsinki, Helsinki, Finland Departments of double daggerOphthalmology, Institute of Clinical Medicine, and section signInternal Medicine, Clinical Research Center and Biocenter Oulu, University of Oulu, Oulu, Finland paragraph signDepartment of Clinical Chemistry, Oulu University Hospital, Oulu, Finland \*\*Department of Biosciences, University of Helsinki, Helsinki, Finland.

**RESUMEN / SUMMARY:** - PURPOSE:: To study the association of single-nucleotide polymorphisms of interleukin 8, vascular endothelial growth factor, erythropoietin, complement factor H, complement component C3, and LOC387715 genes with the response to bevacizumab treatment in exudative age-related macular degeneration. METHODS:: Clinical records, smoking history, optical coherence tomography, and angiographies of 96 bevacizumab-treated exudative age-related macular degeneration patients were analyzed retrospectively. Blood DNA was collected. Based on the disappearance of intra- or subretinal fluid in optical coherence tomography, patients were graded as responders, partial responders, or nonresponders after 3 initial treatment visits and a median time of 3.5 months. RESULTS:: Interleukin 8 promoter polymorphism -251A/T was significantly associated with persisting fluid in optical coherence tomography. The A allele was more frequent in nonresponders than in responders ( $P = 0.033$ ). In multivariate modeling, the AA genotype of -251A/T ( $P = 0.043$ ) and occult ( $P = 0.042$ ) or predominantly classic ( $P = 0.040$ ) lesions predicted poorer outcome. Visual acuity change was better in responders than in nonresponders ( $P = 0.006$ ). Baseline lesion size ( $P = 0.006$ ) and retinal cysts after the treatment ( $P < 0.001$ ) correlated with less visual acuity gain. CONCLUSION:: The A allele and the homozygous AA genotype of interleukin 8 -251A/T were associated with anatomical nonresponse to bevacizumab treatment.

[716]

**TÍTULO / TITLE:** - Apocynin, an NADPH oxidase inhibitor, suppresses progression of prostate cancer via Rac1 dephosphorylation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Toxicol Pathol. 2013 May 9. pii: S0940-2993(13)00045-6. doi: 10.1016/j.etp.2013.03.002.

●●Enlace al texto completo (gratis o de pago) [1016/j.etp.2013.03.002](https://doi.org/10.1016/j.etp.2013.03.002)

**AUTORES / AUTHORS:** - Suzuki S; Pitchakarn P; Sato S; Shirai T; Takahashi S

**INSTITUCIÓN / INSTITUTION:** - Department of Experimental Pathology and Tumor Biology, Graduate School of Medicine, Nagoya City University, Nagoya, Japan; Pathology Division, Nagoya City East Medical Center, Nagoya, Japan.  
Electronic address: [shugo@med.nagoya-cu.ac.jp](mailto:shugo@med.nagoya-cu.ac.jp).

**RESUMEN / SUMMARY:** - Recently, considerable evidence has been generated that oxidative stress contributes to the etiology and pathogenesis of prostate cancer. The present study focused on the effects of apocynin, an inhibitor of the NADPH oxidase which generates intracellular superoxide, on a rat androgen-independent prostate cancer cell line (PLS10) in vitro and in vivo. Apocynin significantly inhibited cell proliferation of PLS10 cells via G1 arrest of the cell cycle in vitro. Surprisingly, it did not affect reactive oxygen species (ROS) but inhibited phosphorylation of Rac1, one component of the NADPH oxidase complex. A Rac1 inhibitor, NSC23766, also inhibited cell proliferation, and both apocynin and NSC23766 reduced phosphorylation of Rac1 and NF-kappaB, as well as cyclin D1. Furthermore, in a xenograft model of prostate cancer with PLS10, apocynin suppressed tumor growth and metastasis in a dose dependent manner in vivo, with reduction of cell proliferation and vessel number in the tumors. Expression and secretion of vascular endothelial growth factor (VEGF) were reduced by apocynin treatment in vivo and in vitro, respectively. In conclusion, despite no apparent direct relationship with oxidative stress, apocynin inhibited growth of androgen-independent prostate cancer in vitro and in vivo. Apocynin thus warrants further attention as a potential anti-tumor drug.

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[717]

**TÍTULO / TITLE:** - Circulating microRNA-21 as noninvasive predictive biomarker for response in cancer immunotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Hypotheses. 2013 May 10. pii: S0306-9877(13)00110-2. doi: 10.1016/j.mehy.2013.03.001.

●●Enlace al texto completo (gratis o de pago)

[1016/j.mehy.2013.03.001](http://1016/j.mehy.2013.03.001)

**AUTORES / AUTHORS:** - Wang Z; Han J; Cui Y; Fan K; Zhou X

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Shandong University School of Medicine, Jinan 250012, Shandong, PR China; Shandong Medicinal Biotechnology Center, Key Laboratory for Biotech-Drugs, Ministry of Health, Shandong Academy of Medical Sciences, Jinan 250062, Shandong, PR China.

**RESUMEN / SUMMARY:** - A pre-existing T cell-inflamed tumor microenvironment is predictive of clinical outcome to immunotherapy, but the mechanisms of immune effector cells infiltration of tumors are not clear. MicroRNAs are a class of small non-coding RNAs that regulate gene expression at the posttranscriptional level. Additionally, circulating miRNAs might be useful as noninvasive biomarkers of disease and therapy response. Previous studies

indicate that STAT3 activity in tumor cells affects immune cells recruitment, which is prerequisite for effective T cell therapy. MiRNA-21 is one of the cell-free miRNAs that has recently been identified as a potential regulator of STAT3. Meanwhile, miRNA-21 is an oncogenic miRNA that could be detected in various tumors. Therefore, we get the hypotheses that circulating miRNA-21 is a potential predictive biomarker for response in cancer immunotherapy and so a novel therapeutic target.

[718]

**TÍTULO / TITLE:** - Could interleukin-15 potentiate histone deacetylase inhibitor effects in haematological malignancy?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Hypotheses. 2013 May 10. pii: S0306-9877(13)00191-6. doi: 10.1016/j.mehy.2013.04.021.

●●Enlace al texto completo (gratis o de pago)

[1016/j.mehy.2013.04.021](#)

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**RESUMEN / SUMMARY:** - Despite significant progress in cancer therapy, prognosis in acute leukaemia remains dismal, and the development of new therapies is urgently warranted: in acute myeloid leukaemia, the current cure rate is of 30-40% in younger and much less in older patients. Chromatin remodeling through histone acetylation is one of the major mechanisms of transcriptional control of genes, and is involved in 'gene silencing' of antioncogenes in various tumour cells. Chromatin remodeling is also involved in transcriptional control of other genes, such as NKG2D ligand genes. Histone deacetylases and acetyltransferases are involved in the epigenetic regulation of gene expression, and increased/decreased activity of histone deacetylases has been reported in several cancer types. Histone deacetylase inhibitors were reportedly active in many cancers including hematological malignancies, and have been shown in numerous experiments to reduce cancer cell growth and enhance cell differentiation, growth arrest and apoptosis. In acute myeloid leukaemia, histone deacetylase inhibitors alone had limited efficacy, but their combination with other anticancer agents yielded promising results. Interleukin (IL)-15 is regarded with great hope in the immunotherapy of cancer, and IL-15-activated cytokine-induced killer cells showed potent antileukemic activity both in vitro and in vivo. IL-15 increases expression of NKG2D and its ligands and can increase natural killer cell mediated cytotoxicity against tumour cells. The administration of IL-15 was recently shown to be safe in preclinical models, and there are ongoing clinical trials of IL-15 in patients with cancer and HIV infection. We hypothesise that IL-15 will synergise with histone deacetylase

inhibitors in increasing the levels of activatory NKG2D receptors on natural killer and CD8+ T cells and of their ligands, the MHC class I related molecule A and B, on tumor cells, and will enhance innate immune antitumour responses in acute myeloid leukaemia and other haematological malignancies. Up-regulation of NKG2D-NKG2D-ligand antitumour immune response by combining histone deacetylase inhibitors with IL-15 has the potential to improve the efficacy of acute myeloid leukaemia treatment.

[719]

**TÍTULO / TITLE:** - Linear Regression of Postevacuation Serum Human Chorionic Gonadotropin Concentrations Predicts Postmolar Gestational Trophoblastic Neoplasia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 May 24.

●●Enlace al texto completo (gratis o de pago)

[1097/IGC.0b013e31829703ea](#)

**AUTORES / AUTHORS:** - Lybol C; Sweep FC; Ottevanger PB; Massuger LF; Thomas CM

**INSTITUCIÓN / INSTITUTION:** - Department of \*Obstetrics and Gynaecology, daggerLaboratory Medicine, and double daggerMedical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Currently, human chorionic gonadotropin (hCG) follow-up after evacuation of hydatidiform moles is essential to identify patients requiring chemotherapeutic treatment for gestational trophoblastic neoplasia (GTN). We propose a model based on linear regression of postevacuation serum hCG concentrations for the prediction of GTN. **METHODS:** One hundred thirteen patients with at least 3 serum samples from days 7 to 28 after evacuation were selected from the Dutch Central Registry for Hydatidiform Moles (1994-2009). The slopes of the linear regression lines of the first 3 log-transformed serum hCG and free beta-hCG values were calculated. Receiver operating characteristic curves were constructed to calculate areas under curve (AUCs). **RESULTS:** The slope of the hCG regression line showed an AUC of 0.906 (95% confidence interval, 0.845-0.967). Gestational trophoblastic neoplasia could be predicted in 52% of patients with GTN at 97.5% specificity (cutoff, -0.020). Twenty-one percent of patients with GTN could be predicted before diagnosis according to the International Federation of Gynecology and Obstetrics 2000 criteria. The slope of free beta-hCG showed an AUC of 0.844 (95% confidence interval, 0.752-0.935), 69% sensitivity at 97.5% specificity, and 38% of patients with GTN could be predicted before diagnosis according to the International Federation of Gynecology and Obstetrics criteria. **CONCLUSIONS:** The slope of the linear regression line of hCG proved to be a good test to discriminate between patients who will achieve spontaneous disease remission and patients developing GTN. The slope of free

beta-hCG seems to be a better predictor for GTN than the slope of hCG. Although this model needs further validation for different assays, it seems a promising way to predict the more aggressive cases of GTN.

[720]

**TÍTULO / TITLE:** - Preemptive intravenous immunoglobulin allows safe and timely administration of antineoplastic therapies in patients with multiple myeloma and parvovirus B19 disease.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Transpl Infect Dis. 2013 Apr 11. doi: 10.1111/tid.12067.

●●Enlace al texto completo (gratis o de pago) [1111/tid.12067](#)

**AUTORES / AUTHORS:** - Katragadda L; Shahid Z; Restrepo A; Muzaffar J; Alapat D; Anaissie E

**INSTITUCIÓN / INSTITUTION:** - The Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Parvovirus B19 (B19) disease is a rare cause of anemia in cancer patients and often goes unrecognized, causing delays in anticancer therapy. METHODS: A retrospective review was carried out of the records of patients with multiple myeloma who underwent melphalan-based autologous stem cell transplantation (MEL-ASCT) and developed B19 infection (January 2009-December 2011). Cases were defined by the presence of clinical and laboratory findings consistent with B19 disease in patients with repeatedly positive plasma quantitative polymerase chain reaction for parvovirus. RESULTS: Six patients qualified as cases; 5 presented with trilineage cytopenias (chronic in 1) and 1 with anemia later progressing to pancytopenia. Transfusion-dependent thrombocytopenia led to testing in 5 patients. Two of these patients also had manifestations of autoimmune disease. Therapy with intravenous immunoglobulin (IVIG) resulted in clinical and hematologic response in all; however, 1 patient, whose white blood cell counts and serum hemoglobin levels improved, required splenectomy for persistent thrombocytopenia. All patients required additional IVIG for recurrent B19 disease. Although viral load at diagnosis did not correlate with the severity of cytopenia, its decrease was associated with response during 17 of 20 evaluable episodes (P = 0.02). Preemptive IVIG allowed the safe administration of chemotherapy in 3 patients, including MEL-ASCT in 1. CONCLUSION: Parvovirus B19 can cause severe disease in myeloma patients including ASCT recipients. Thrombocytopenia - not anemia - was the leading presentation and may be associated with autoimmune conditions. Patients with unexplained cytopenias, particularly when prolonged, should undergo testing for circulating parvovirus. A reduction in viral load was associated with response to IVIG, although additional therapy was needed for recurrent disease. Most importantly, preemptive IVIG allowed for safe and timely administration of antineoplastic therapy in patients with ongoing B19 disease.

[721]

**TÍTULO / TITLE:** - Protein-coding genes and long noncoding RNAs are differentially expressed in dasatinib-treated chronic myeloid leukemia patients with resistance to imatinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematology. 2013 May 9.

●●Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000094](#)

**AUTORES / AUTHORS:** - Silveira RA; Fachel AA; Moreira YB; De Souza CA; Costa FF; Verjovski-Almeida S; Pagnano KB

**RESUMEN / SUMMARY:** - Dasatinib has demonstrated efficacy in patients with chronic-phase chronic myeloid leukemia (CML) who had resistance or intolerance to imatinib. However, some patients also develop resistance or intolerance to dasatinib. To identify potential molecular pathways involved in primary resistance to dasatinib in CML, we analyzed gene expression profiles of mononuclear cells of 7 imatinib-resistant patients, collected before and after 1-year dasatinib treatment. Large-scale gene expression was measured with Agilent microarrays covering protein-coding genes and long (>200 nt) noncoding RNAs (lncRNAs). Sets of genes and lncRNAs significantly differentially expressed (>1.5 fold-change; q value <=10%) were identified. Ingenuity Pathway Analysis pointed to a number of functions, canonical pathways and gene networks that were significantly enriched with differentially expressed genes. In addition to protein-coding genes, lncRNAs have been recently implicated in pathways leading to tumorigenesis. Our data point to new possible regulatory elements involved in dasatinib resistance in CML.

[722]

**TÍTULO / TITLE:** - Disease Flare After EGFR Tyrosine Kinase Inhibitor Cessation Predicts Poor Survival in Patients with Non-small Cell Lung Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s12253-013-9651-](#)

[Z](#)

**AUTORES / AUTHORS:** - Chen HJ; Yan HH; Yang JJ; Chen ZH; Su J; Zhang XC; Wu YL

**INSTITUCIÓN / INSTITUTION:** - Division of Pulmonary Oncology, Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, People's Republic of China.

**RESUMEN / SUMMARY:** - Available study revealed non-small cell lung cancer (NSCLC) patients faced a risk of disease flare after cessation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment. There

was no data concerning the prognostic value of disease flare. This study aimed to investigate the prevalence of disease flare in a Chinese cohort, and analyzed its prediction to survival. A cohort of 227 NSCLC patients with acquired resistance to EGFR TKI was retrospectively analyzed. Prevalence and clinical features of disease flare after TKI cessation were reviewed. Survival data were analyzed between patients with flare and those without flare. EGFR gene mutations in tumors were detected. Twenty of 227 (8.8 %) patients were determined with disease flare after TKI cessation. The median interval from TKI cessation to disease flare was 7 days (range 3-18). Forty percent of patients complained of deteriorated dyspnea attributable to malignant effusion. Thirty percent of patients had progressive lesions in the brain. After TKI cessation 35 % of flare patients died before challenge of subsequent treatment. No response was observed in 30 % of flare patients undergoing subsequent chemotherapy. When compared with the non-flare group, patients with disease flare demonstrated comparable progression-free survival (10.1 vs. 9.9 months; P = 0.973), shorter post-TKI survival (4.1 vs. 6.1 months; P < 0.001), and a significantly poor overall survival (16.6 vs. 21.6 months; P = 0.002). Disease flare after cessation of EGFR TKI occurred in Chinese NSCLC population and predicted a poor survival.

[723]

**TÍTULO / TITLE:** - The cyclin D1 (CCND1) rs9344 G>A polymorphism predicts clinical outcome in colon cancer patients treated with adjuvant 5-FU-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics J. 2013 Apr 9. doi: 10.1038/tpj.2013.15.

●●Enlace al texto completo (gratis o de pago) [1038/tpj.2013.15](#)

**AUTORES / AUTHORS:** - Absenger G; Benhaim L; Szkandera J; Zhang W; Yang D; Labonte MJ; Pichler M; Stotz M; Samonigg H; Renner W; Gerger A; Lenz HJ

**INSTITUCIÓN / INSTITUTION:** - 1] Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria [2] Research Unit Genetic Epidemiology and Pharmacogenetics, Medical University of Graz, Graz, Austria [3] Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria.

**RESUMEN / SUMMARY:** - Recent evidence indicates a potential prognostic and predictive value for germline polymorphisms in genes involved in cell cycle control. We investigated the effect of cyclin D1 (CCND1) rs9344 G>A in stage II/III colon cancer patients and validated the findings in an independent study cohort. For evaluation and validation set, a total of 264 and 234 patients were included. Patients treated with 5-fluorouracil-based chemotherapy, carrying the CCND1 rs9344 A/A genotype had significantly decreased time-to-tumor recurrence (TTR) in univariate analysis and multivariate analysis (hazard ratio

(HR) 2.47; 95% confidence interval (CI) 1.16-5.29; P=0.019). There was no significant association between CCND1 rs9344 G>A and TTR in patients with curative surgery alone. In the validation set, the A allele of CCND1 rs9344 G>A remained significantly associated with decreased TTR in univariate and multivariate analyses (HR 1.94; 95% CI 1.05-3.58; P=0.035). CCND1 rs9344 G>A may be a predictive and/or prognostic biomarker in stage II/III colon cancer patients, however, prospective trials are warranted to confirm our findings. The Pharmacogenomics Journal advance online publication, 9 April 2013; doi:10.1038/tpj.2013.15.

[724]

**TÍTULO / TITLE:** - Predictive Effect of XPA and XPD Polymorphisms on Survival of Advanced NSCLC Patients Treated with Platinum-based Chemotherapy: A Three-dimensional (3-D), Polyacrylamide Gel-Based DNA Microarray Method.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Technol Cancer Res Treat. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [7785/tcrt.2012.500337](#)

**AUTORES / AUTHORS:** - Cheng H; Qin Q; Sun X; Li F; Sun N; Cheng L; Lu Z; Chen B

**INSTITUCIÓN / INSTITUTION:** - Medical School, Southeast University, Nanjing 210009, China. [shuizhuqq@yahoo.cn](mailto:shuizhuqq@yahoo.cn).

**RESUMEN / SUMMARY:** - Platinum-based chemotherapy is a primary treatment for patients with advanced non-small cell lung cancer (NSCLC). Considering individual differences, an effective and convenient method is urgently needed to identify the sensitivity of individual patient to platinum based regimen. Genetic variants in DNA repair genes are presumed to represent important determinants of drug efficacy. Our previous studies have demonstrated the involvement of xeroderma pigmentosum group A (XPA) codon23 and xeroderma pigmentosum group D (XPD) codon751 single-nucleotide polymorphisms (SNPs) in clinical response to platinum based chemotherapy in advanced NSCLC patients. Thus, a follow-up study was carried out to investigate the relevance of these genotypes and survival of the cohort (n = 115). The three-dimensional (3-D), polyacrylamide gel-based DNA microarray method was used to assess the genotypes of XPA and XPD in peripheral lymphocytes. Log-rank test revealed that the variant genotypes of XPA23 (A/G+G/G) were associated with significantly longer progression-free survival (PFS) (6.0 m vs. 10.6 m, log-rank P = 0.001) and overall survival (OS) (11.2 m vs. 20.8 m, log-rank P = 0.001). In Cox proportional hazards model, the hazard ratio (HR) for death in patients with G allele was 0.65 (P = 0.049). While no significant differences were observed in PFS or OS according to XPD Lys751Gln genotypes (log-rank P > 0.05). In combination with our previous short-term clinical results, this study further confirmed that by detecting the SNPs in blood cells, XPA A23G polymorphic

variants might be a promising biomarker in predicting a favor prognosis of NSCLC patients and be helpful towards designing individualized treatments.

[725]

**TÍTULO / TITLE:** - D-index dose not predict the development of pulmonary infection in acute myeloid leukemia patients undergoing consolidation chemotherapy with high-dose cytarabine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematology. 2013 May 16.

●●Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000103](#)

**AUTORES / AUTHORS:** - Kimura SI; Wada H; Ishihara Y; Kawamura K; Sakamoto K; Yamasaki R; Ashizawa M; Machishima T; Sato M; Terasako K; Nakasone H; Kikuchi M; Okuda S; Kako S; Kanda J; Yamazaki R; Tanihara A; Nishida J; Kanda Y

**RESUMEN / SUMMARY:** - The D-index is calculated as the area over the neutrophil curve during neutropenia. We investigated the impact of the D-index on pulmonary infection in 33 acute myeloid leukemia patients undergoing consolidation chemotherapy with high-dose cytarabine. There was no difference in the D-index between chemotherapies with and without pulmonary infection. The cumulative D-index (c-D-index) until the development of infection exceeded 4000 in four of five patients with pulmonary infection. Although there was no difference in the total D-index throughout the overall consolidation chemotherapy, the total D-index from induction to consolidation and the D-index at induction chemotherapy were higher in patients with pulmonary infection during consolidation than in those without it (P = 0.014 and 0.019, respectively). Our results showed that the cumulative effect of neutropenia might determine the risk of pulmonary infection in consolidation chemotherapy. We are planning a clinical trial of c-D-index-guided preemptive antifungal therapy.

[726]

**TÍTULO / TITLE:** - Association of MDR1 gene polymorphism (G2677T) with imatinib response in Egyptian chronic myeloid leukemia patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematology. 2013 May 16.

●●Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000102](#)

**AUTORES / AUTHORS:** - Elghannam DM; Ibrahim L; Ebrahim MA; Azmy E; Hakem H

**RESUMEN / SUMMARY:** - BACKGROUND: Despite the excellent efficacy results of imatinib treatment in CML patients, resistance to imatinib has emerged as a significant problem. Genetic variations in genes involved in drug transportation

might influence the pharmacokinetic and metabolism of imatinib. The genotype of a patient is increasingly recognized in influencing the response to the treatment. AIM: To investigate the genotype frequencies of single nucleotide polymorphisms (SNPs) G2677T in CML patients undergoing imatinib treatment to determine whether different genotype pattern of these SNPs have any influence in mediating response to imatinib. METHODS: A total of 96 CML and 90 control samples were analyzed for the human multidrug resistance gene 1 (MDR1) gene polymorphism (G2677T) using polymerase chain reaction-restriction fragment length polymorphism technique. RESULTS: Genotype distribution revealed a significant lower frequency of TT genotype in CML patients and non-significant difference in the GG, GT genotype frequencies between patients and controls ( $P = 0.004, 0.138, 0.210$ , respectively). GG genotype was significantly higher in chronic phase ( $P = 0.046$ ), while GT genotype was significantly higher in Blastic crisis phase ( $P = 0.002$ ). There was a significant difference in genotype frequency of G2677T among patients showing response and resistance to imatinib in chronic phase ( $P = 0.02$ ). TT genotype was associated with complete hematological response ( $P = 0.01$ ), complete cytogenetic response ( $P < 0.001$ ), and better molecular response with a significant association ( $P < 0.001$ ). GT genotype was associated with partial hematological response ( $P = 0.01$ ) and minor cytogenetic response ( $P < 0.001$ ). Optimal and suboptimal responses were observed for patients with TT genotype ( $P = 0.003$ ). Failure of drug response was associated with GT genotype ( $P = 0.02$ ); however, GG had no association with drug response. Multivariate analysis considered GT genotype as independent risk factor for resistance ( $P = 0.037$ ), while TT genotype as protective factor against resistance to imatinib ( $P = 0.008$ ). CONCLUSION: Determination of MDR1 polymorphisms (G2677T) might be useful in response prediction to therapy with imatinib in patients with CML.

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[727]

**TÍTULO / TITLE:** - Impact of the CYP2D6 phenotype on the outcome of breast cancer patients treated with tamoxifen.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Apr;14(6):606.

**AUTORES / AUTHORS:** - Dorado P; Penas-Lledo E; LLerena A

**INSTITUCIÓN / INSTITUTION:** - CICAB, Clinical Research Centre, Extremadura University Hospital & Medical School, Badajoz 06080, España.

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[728]

**TÍTULO / TITLE:** - Is TIMP-1 immunoreactivity alone or in combination with other markers a predictor of benefit from anthracyclines in the BR9601 adjuvant breast cancer chemotherapy trial?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res. 2013 Apr 9;15(2):R31.

●●Enlace al texto completo (gratis o de pago) [1186/bcr3411](#)

**AUTORES / AUTHORS:** - Munro AF; Bartels A; Balslev E; Twelves CJ; Cameron DA; Brunner N; Bartlett JM

**INSTITUCIÓN / INSTITUTION:** - Transformative Pathology, Ontario Institute for Cancer Research, MaRS Centre, South Tower, 101 College Street, Suite 800, Toronto, ON M5G 0A3, Canada. [John.Bartlett@oicr.on.ca](mailto:John.Bartlett@oicr.on.ca).

**RESUMEN / SUMMARY:** - INTRODUCTION: Predictive cancer biomarkers to guide the right treatment to the right patient at the right time are strongly needed. The purpose of the present study was to validate prior results that tissue inhibitor of metalloproteinase 1 (TIMP-1) alone or in combination with either HER2 or TOP2A copy number can be used to predict benefit from epirubicin (E) containing chemotherapy compared with cyclophosphamide, methotrexate and fluorouracil (CMF) treatment. METHODS: For the purpose of this study, formalin fixed paraffin embedded tumor tissue from women recruited into the BR9601 clinical trial, which randomized patients to E-CMF versus CMF, were analyzed for TIMP-1 immunoreactivity. Using previously collected data for HER2 amplification and TOP2A gene aberrations, we defined patients as "anthracycline non-responsive", that is, 2T (TIMP-1 immunoreactive and TOP2A normal) and HT (TIMP-1 immunoreactive and HER2 negative) and anthracycline responsive (all other cases). RESULTS: In total, 288 tumors were available for TIMP-1 analysis with (183/274) 66.8%, and (181/274) 66.0% being classed as 2T and HT responsive, respectively. TIMP-1 was neither associated with patient prognosis (relapse free survival or overall survival) nor with a differential effect of E-CMF and CMF. Also, TIMP-1 did not add to the predictive value of HER2, TOP2A gene aberrations, or to Ki67 immunoreactivity. CONCLUSION: This study could not confirm the predictive value of TIMP-1 immunoreactivity in patients randomized to receive E-CMF versus CMF as adjuvant treatment for primary breast cancer.

[729]

**TÍTULO / TITLE:** - Detection of BCR-ABL kinase domain mutations in patients with chronic myeloid leukemia on imatinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematology. 2013 May 8.

●●Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000095](#)

**AUTORES / AUTHORS:** - Chahardouli B; Zaker F; Mousavi SA; Saffari Z; Nadali F; Ostadali M; Ghadimi H; Alimoghaddam K; Ghavamzade A; Rostami S

**RESUMEN / SUMMARY:** - BCR-ABL tyrosine kinase domain mutations are the most important factor contributing to imatinib-resistance in patients with chronic myeloid leukemia. We used a semi-nested reverse transcriptase-polymerase chain reaction followed by bidirectional sequencing to detect mutations in a cohort of 110 chronic myeloid leukemia patients. In total, 34 mutations in 19 distinct codons were identified in 32 patients, of which D276N and E279A were novel. The most commonly mutated region was drug-binding site (29%) followed by P-loop region (26%) and most patients bearing them were in accelerated phase and blastic phase. This report expands the spectrum of BCR-ABL mutations and stresses the use of mutation testing in imatinib-resistant patients for continuation of treatment procedure.

[730]

**TÍTULO / TITLE:** - Low-dose cytarabine and aclarubicin combined with granulocyte colony-stimulating factor for the treatment of relapsed or primary refractory acute lymphocytic leukemia: a retrospective study of 25 Chinese patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematol Oncol. 2013 Apr 25. doi: 10.1002/hon.2051.

●●Enlace al texto completo (gratis o de pago) [1002/hon.2051](#)

**AUTORES / AUTHORS:** - Xue SL; Cui HX; Zou JY; Xue MX; Tang XW; Zhang YM; Wu DP

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China; Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China; Key Laboratory of Thrombosis and Hemostasis of Ministry of Health, The First Affiliated Hospital of Soochow University, Suzhou, China.

**RESUMEN / SUMMARY:** - Despite improvements in treatment, the prognosis of relapsed or primary refractory acute lymphocytic leukemia (ALL) remains poor, and outcomes are worse in older adults with the short first complete remission (CR). Attainment of the second CR by salvage therapy would improve the survival of these patients and may enable them to undergo curative treatment with allogeneic hematopoietic stem cell transplantation. The fact that there are diverse salvage protocols for these adult patients but without a striking CR-induction efficacy indicates that efforts are still needed to identify new effective reinduction regimens. In this study, the CAG regimen (cytarabine, 10 mg/m<sup>2</sup> subcutaneously every 12 h on days 1-14; aclarubicin, 5-7 mg/m<sup>2</sup> intravenously daily on days 1-8; and concurrent granulocyte colony-stimulating factor, 200 microg/m<sup>2</sup> /day subcutaneously) was administered to 25 patients with relapsed or refractory ALL, including 11 T-cell ALL (T-ALL) and 14 B-cell (B-ALL) patients (age range, 11-61 years; median age, 26 years), to assess its efficacy as a salvage therapy. One course of the CAG regimen resulted in an overall response [CR or partial remission (PR)] rate of 64%, a CR rate of 56% and

generally mild adverse effects. An overall response was observed in all 11 T-ALL patients (10 CR and 1 PR) and 35.7% of B-ALL patients ( $p = 0.0009$ ). The significant treatment potential of CAG regimen for relapsed or primary refractory ALL, especially for T-ALL patients, described in this report would prepare them for a second CR to pursue longer survival. Copyright © 2013 John Wiley & Sons, Ltd.

[731]

**TÍTULO / TITLE:** - DNA repair and cytotoxic drugs: the potential role of RAD51 in clinical outcome of non-small-cell lung cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Apr;14(6):689-700. doi: 10.2217/pgs.13.48.

●●Enlace al texto completo (gratis o de pago) [2217/pgs.13.48](#)

**AUTORES / AUTHORS:** - Nogueira A; Assis J; Catarino R; Medeiros R

**INSTITUCIÓN / INSTITUTION:** - Portuguese Institute of Oncology, Molecular Oncology Group - CI, Edifícios Laboratórios - Piso 4, Rua Dr. Ant. Bernardino Almeida, 4200-072 Porto, Portugal.

**RESUMEN / SUMMARY:** - Many of the cytotoxic drugs used in the treatment of non-small-cell lung carcinoma patients can interfere with DNA activity and the definition of an individual DNA repair profile could be a key strategy to achieve better response to chemotherapeutic treatment. Although DNA repair mechanisms are important factors in the prevention of carcinogenesis, these molecular pathways are also involved in therapy response. RAD51 is a crucial element in DNA repair by homologous recombination and has been shown to interfere with the prognosis of patients treated with chemoradiotherapy. There is increasing evidence that genetic polymorphisms in repair enzymes can influence DNA repair capacity and, consequently, affect chemotherapy efficacy. We conducted this review to show the possible influence of the RAD51 genetic variants in damage repair capacity and treatment response in non-small-cell lung carcinoma patients.

[732]

**TÍTULO / TITLE:** - Evaluation of T315I mutation frequency in chronic myeloid leukemia patients after imatinib resistance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematology. 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago)

[1179/1607845412Y.0000000050](#)

**AUTORES / AUTHORS:** - Chahardouli B; Zaker F; Mousavi SA; Kazemi A; Ostadali M; Nadali F; Rostami S; Alimoghaddam K; Ghavamzade A

**RESUMEN / SUMMARY:** - The occurrence of resistance mutations in the Abl kinase domain plays a central role in drug treatment failure in chronic myeloid leukemia (CML) patients. Among them, the T315I mutation at the gatekeeper position affects a common Abl kinase contact residue and confers complete resistance to all known ATP-competitive BCR-ABL inhibitors. In the present study, an allele-specific oligonucleotide reverse transcriptase polymerase chain reaction assay was used to detect T315I mutation in a cohort of 60 imatinib-resistant CML patients. In terms of disease phase, 43 patients (71%) were in late chronic phase, 4 (7%) in accelerated phase, and 13 (22%) in blastic phase. The prevalence of the T315I mutation was found to be 7% (4/60). All four patients with mutation were in advance phases and had previously lost all their responses. The results of the study confirmed that this method is low cost and easy tool to operate for T315I mutation screening and direct sequencing should be performed in positive cases for confirmation.

[733]

**TÍTULO / TITLE:** - Development of an Epstein-Barr virus-associated lymphoproliferative disorder in a patient treated with azacitidine for chronic myelomonocytic leukaemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematol Oncol. 2013 Apr 29. doi: 10.1002/hon.2054.

●●Enlace al texto completo (gratis o de pago) [1002/hon.2054](#)

**AUTORES / AUTHORS:** - Menter T; Schlageter M; Bastian L; Haberthur R; Ratz Bravo A; Tzankov A

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, University Hospital Basel, Basel, Switzerland.

**RESUMEN / SUMMARY:** - Some chemotherapeutic agents can cause iatrogenic lymphoproliferative disorders. In analogy to what has been observed with other nucleoside analogues such as cladribine and fludarabine, we document the first case of an Epstein-Barr virus-positive, iatrogenic immunodeficiency-associated, lymphoproliferative disease, formally resembling polymorphic post-transplant lymphoproliferative disease in a patient treated with azacitidine (Vidaza) for chronic myelomonocytic leukaemia (CMML). A 78-year-old female patient was diagnosed with CMML in January 2012, and treatment with azacitidine was initiated, which lasted for five cycles from February until June 2012. The patient was hospitalized in June 2012 under the suspicion of pneumonia. Transformation of the CMML was suspected at that time too. During hospitalization, a generalized enlargement of the lymph nodes and the spleen was noticed. The patient rapidly deteriorated and finally died of respiratory insufficiency. At autopsy, an Epstein-Barr virus-associated lymphoproliferative disorder, resembling polymorphic post-transplant lymphoproliferative disease with involvement of the lymph nodes, the spleen and the lung and causing necrotizing pneumonia, was diagnosed. Diagnostic criteria for diffuse large B-

cell lymphoma or infectious mononucleosis-like lymphoproliferative disease were not met. This is the first documented case of an azacitidine-associated lymphoproliferative disease, raising awareness for possible not yet known side effects of this drug, which should be kept in mind by oncologists and pathologists. Copyright © 2013 John Wiley & Sons, Ltd.

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[734]

**TÍTULO / TITLE:** - Feasibility and pharmacokinetics of combined therapy with S-1 and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic or recurrent breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Oncol. 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [1007/s10147-013-0547-4](#)

**AUTORES / AUTHORS:** - Suzuki Y; Ogiya R; Oshitanai R; Terao M; Terada M; Morioka T; Tsuda B; Niikura N; Okamura T; Saito Y; Tokuda Y

**INSTITUCIÓN / INSTITUTION:** - Division of Breast and Endocrine Surgery, Department of Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa, 259-1193, Japan, [luke-szk@is.icc.u-tokai.ac.jp](mailto:luke-szk@is.icc.u-tokai.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: To clarify the tolerance and pharmacokinetics of combined therapy with S-1 and trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic or recurrent breast cancer. METHODS: From January 2008 through to September 2009, combined therapy with S-1 and trastuzumab was given to 7 patients with HER2-positive metastatic or recurrent breast cancer. The incidence of adverse events and the pharmacokinetics of tegafur, 5-fluorouracil, and gimeracil in plasma were studied. RESULTS: One patient had grade 3 leukopenia, and another had a grade 3 elevation of alanine aminotransferase. All other adverse events were grade 2 or lower. The combination of S-1 and trastuzumab did not cause any new adverse events. The incidence of adverse events was similar to those associated with S-1 alone. The median number of treatment cycles was 11. The pharmacokinetics of tegafur, 5-fluorouracil, and gimeracil after treatment with S-1 plus trastuzumab did not markedly differ from those after S-1 alone. CONCLUSIONS: Combined therapy with S-1 and trastuzumab did not cause any new adverse events, administration continuity was good, and the therapy was well tolerated.

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[735]

**TÍTULO / TITLE:** - A case of delivery of healthy infant in breast cancer patient incidentally treated with goserelin acetate and tamoxifen during pregnancy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer. 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [1007/s12282-013-0469-](http://1007/s12282-013-0469-)

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**AUTORES / AUTHORS:** - Ishizuka S; Satou S

**INSTITUCIÓN / INSTITUTION:** - Ishizuka Breast Surgery Clinic, 3-3-27 Shimoteno, Himeji, Hyogo, 670-0063, Japan, [ishizuka-breast@wing.ocn.ne.jp](mailto:ishizuka-breast@wing.ocn.ne.jp).

**RESUMEN / SUMMARY:** - In September 2000, a 32-year-old woman presented to our hospital with a right breast mass. In September 2000, she underwent pectoral muscle-preserving mastectomy for the treatment of right breast cancer. Pathology results revealed a mucinous carcinoma 27 x 20 x 18 mm in size accompanied by an extensive intraductal component. The tumor was staged as T2 N1M0 stage IIB and found to be estrogen receptor-positive, and 6 cycles of postoperative adjuvant chemotherapy consisting of 5-fluorouracil, epirubicin, and cyclophosphamide were carried out. Goserelin acetate plus tamoxifen was prescribed from April 2001 to March 2005. Since the patient received tamoxifen from April 2005 and eumenorrhea started in June 2006, goserelin acetate plus tamoxifen was started in August 2006. The patient was determined to be 25 weeks pregnant by abdominal ultrasonography in February 2007. This meant that she had been taking goserelin acetate plus tamoxifen for 6 months without realizing she was pregnant. She gave birth to a girl by cesarean section in May 2007. No abnormalities, including anomaly of the genitalia, were seen, and the subsequent growth of the infant was also satisfactory. We here report this case and a brief review of the literature.

[736]

**TÍTULO / TITLE:** - Effect of hypericin on the ADAMTS-9 and ADAMTS-8 gene expression in MCF7 breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur Rev Med Pharmacol Sci. 2013 May;17(9):1185-90.

**AUTORES / AUTHORS:** - Ocak Z; Acar M; Gunduz E; Gunduz M; Demircan K; Uyeturk U; Ozlu T

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Genetics, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey.

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**RESUMEN / SUMMARY:** - AIM: To investigate the effects of hypericin which is obtained from the plant *Hypericum perforatum* on the expression and the regulation of ADAMTS8 and ADAMTS9 genes in MCF7 breast cancer cells and on the viability of these cells. MATERIALS AND METHODS: MCF7 cells were cultured and were separately exposed to 2, 10 and 50 microl/mL of hypericin. After 24 hours, RNA was isolated from these cells and converted to cDNA. The expression levels of ADAMTS8 and ADAMTS9 genes were evaluated using the Reverse Transcription Polymerase Chain Reaction. XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide, disodium salt) cell viability assay was used to determine cytotoxicity. RESULTS: ADAMTS9 expression in

MCF7 cells were increased 1.8 and 3.6 fold with the use of 2 and 10 microl/mL of hypericin, respectively; and decreased 0.7 fold with the use of 50 microl/mL of hypericin. There was no significant change in the ADAMTS8 expression. Rapid cell death was observed in the cancer cells when hypericin was used at a dose of  $\geq$  50 microl/mL. CONCLUSIONS: The increase in ADAMTS9 expression can be a useful factor in the prevention of possible metastasis in breast cancer and for the occurrence of a tumor suppressive effect. Hypericin increases the expression of ADAMTS9, therefore, it may show its antitumoral and antiapoptotic effects by means of ADAMTS9.

[737]

**TÍTULO / TITLE:** - Phase I study of highly selective inhibitor of VEGFR tyrosine kinase, tivozanib, in Japanese patients with solid tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Sci. 2013 May 16. doi: 10.1111/cas.12197.

●●Enlace al texto completo (gratis o de pago) [1111/cas.12197](#)

**AUTORES / AUTHORS:** - Niwakawa M; Yamaguchi R; Onozawa Y; Yasui H; Taku K; Naito T; Akinaga S; Boku N; Yamamoto N

**INSTITUCIÓN / INSTITUTION:** - Division of Urology, Shizuoka Cancer Center.

**RESUMEN / SUMMARY:** - Tivozanib is a potent and selective inhibitor of VEGFR tyrosine kinases. A previous clinical trial in EU and US demonstrated that tivozanib at the MTD dose of 1.5 mg/day showed an antitumor activity in patients with renal cell carcinoma (RCC). This Japanese phase I study was designed to determine the recommended phase II dose of tivozanib in the Japanese population, secondary objectives include PK/PD profiles, and preliminary efficacy. Administration of daily tivozanib in 3-week-on/ 1-week-off cycle was examined in 9 Japanese patients with advanced solid tumors in the 3+3 design (Level 1, 1.0 mg; Level 2, 1.5 mg). No dose-limiting toxicity was observed throughout the study, and the maximum tolerated dose was not reached. The most commonly observed drug-related adverse events were diarrhea, dysphonia, rash, thyroid stimulating hormone increase, and with severity grade  $\geq$ 3, hand-foot skin reaction, hypertension, and proteinuria. Those adverse events were generally well-manageable and mostly resolved within tolerability evaluation period. Serum exposure to tivozanib resulted in  $t_{1/2}$  of more than  $>60$  hours. Increase of plasma VEGF and decrease of plasma VEGFR-1 and VEGFR-2 were observed 1-3 weeks after tivozanib treatment. Although no complete or partial response was observed, long-term stable disease continuing more than 170 days was observed in three RCC patients who had failed prior VEGFR inhibitors. In conclusion, 1.5 mg/day of tivozanib in 3-week-on/ 1-week-off setting was tolerable in Japanese patients, and was recommended for the further clinical trials in Japanese population. Clinical trial Registration No: JapicCTI-090854. This article is protected by copyright. All rights reserved.

[738]

**TÍTULO / TITLE:** - Prognostic factors for outcomes of allogeneic stem cell transplantation in chronic phase chronic myeloid leukemia in the era of tyrosine kinase inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematology. 2013 May 16.

●●Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000100](#)

**AUTORES / AUTHORS:** - Lee SE; Choi SY; Kim SH; Jang EJ; Bang JH; Byeun JY; Park JE; Jeon HR; Oh YJ; Yahng SA; Cho BS; Eom KS; Kim YJ; Lee S; Min CK; Kim HJ; Lee JW; Min WS; Park CW; Kim DW

**RESUMEN / SUMMARY:** - The aim of this study was to estimate the prognostic factors for the outcomes of chronic myeloid leukemia (CML) patients receiving allogeneic stem cell transplantation (SCT) in chronic phase (CP) in the era of tyrosine kinase inhibitors (TKIs). Ninety-seven patients who underwent allogeneic SCT in CP were analyzed. Forty-seven were TKI-naïve at the time of transplant, and 50 received TKI(s) treatment before transplantation. After a median follow-up of 115.8 months, the 4-year overall survival and event-free survival were 80.4 and 58.8%, respectively. Multivariate analysis showed that there were no differences in survival outcomes based on prior TKI therapy. Older age was a prognostic factor for higher treatment-related mortality (TRM), and the type of graft source and younger age were associated with relapse, but prior TKI therapy and disease status at the time of transplant were not associated with either TRM or relapse. Additionally, a major molecular response at 1 month and an MR4.5 at 3 months were important predictors of favorable long-term outcomes. This study demonstrates the prognostic factors for the outcomes of allogeneic SCT in CP CML and shows that survival outcomes were not affected by the administration of long-term multi-TKI treatment prior to transplantation.

[739]

**TÍTULO / TITLE:** - Higher frequency of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, AIDS and tuberculosis in persons of African descent.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics J. 2013 Apr 16. doi: 10.1038/tpj.2013.13.

●●Enlace al texto completo (gratis o de pago) [1038/tpj.2013.13](#)

**AUTORES / AUTHORS:** - Aminkeng F; Ross CJ; Rassekh SR; Brunham LR; Sistonen J; Dube MP; Ibrahim M; Nyambo TB; Omar SA; Froment A; Bodo JM; Tishkoff S; Carleton BC; Hayden MR

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.

**RESUMEN / SUMMARY:** - There is established clinical evidence for differences in drug response, cure rates and survival outcomes between different ethnic populations, but the causes are poorly understood. Differences in frequencies of functional genetic variants in key drug response and metabolism genes may significantly influence drug response differences in different populations. To assess this, we genotyped 1330 individuals of African (n=372) and European (n=958) descent for 4535 single-nucleotide polymorphisms in 350 key drug absorption, distribution, metabolism, elimination and toxicity genes. Important and remarkable differences in the distribution of genetic variants were observed between Africans and Europeans and among the African populations. These could translate into significant differences in drug efficacy and safety profiles, and also in the required dose to achieve the desired therapeutic effect in different populations. Our data points to the need for population-specific genetic variation in personalizing medicine and care. *The Pharmacogenomics Journal* advance online publication, 16 April 2013; doi:10.1038/tpj.2013.13.

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[740]

**TÍTULO / TITLE:** - Research on aromatase gene (CYP19A1) polymorphisms as a predictor of endocrine therapy effectiveness in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Rev Med Chir Soc Med Nat Iasi*. 2012 Oct-Dec;116(4):997-1004.

**AUTORES / AUTHORS:** - Miron L; Negura L; Peptanariu D; Marinca M

**INSTITUCIÓN / INSTITUTION:** - University of Medicine and Pharmacy Grigore T Popa Iasi, Faculty of Medicine.

**RESUMEN / SUMMARY:** - Single nucleotide polymorphisms (SNPs) of the CYP19A1 gene have shown the ability to modify its activity, but no association has been established with aromatase inhibitor (AI) efficiency in hormone receptor positive breast cancer (BC). **MATERIAL AND METHODS:** The study included blood samples from 53 patients (p) with BC and 1 control (male DNA); 22p. (investigational group) were administered an AI and followed up. **RESULTS:** Homozygous (hh) -CC and TT -, and heterozygous (hz) - TC - genotypes of the rs10046 SNP were balanced. Response to treatment or progression were not affected (p=0.630) in patients with T allele 1; local relapse occurred significantly more rarely and overall survival (OS) was superior (p=0.046). For rs4646, genotypes were mainly hhGG (57%), with no implication to study parameters (p>0.05). For rs727479 SNP, major genotypes were hhTT (40%) and hzTG (45%). Therapeutic response was better in patients with T allele 2 (p=0.040), T allele 1 was associated with reduced local recurrence (p=0.047) and TT genotype with better OS (p = 0.008). In rs700518 SNP,

genotype was mostly hzGA (49%). Local recurrence rates were reduced in the presence of G allele 1 ( $p=0.047$ ) and GG homozygosity. CONCLUSIONS: At this stage, the study was purely exploratory and hypothesis generating. Genotyping of at least three of the four CYP19A1 SNPs evaluated (except rs4646) may have an impact in clinical practice, providing better criteria for patient selection, prognosis and therapeutic decision in BC.

[741]

**TÍTULO / TITLE:** - Prediction of BRCA1 Germ-Line Mutation Status in Patients with Breast Cancer Using Histoprognosis Grade, MS110, Lys27H3, Vimentin, and KI67.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathobiology. 2013;80(5):219-27. doi: 10.1159/000339432. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1159/000339432](#)

**AUTORES / AUTHORS:** - Hassanein M; Huiart L; Bourdon V; Rabayrol L; Geneix J; Nogues C; Peyrat JP; Gesta P; Meynard P; Dreyfus H; Petrot D; Lidereau R; Noguchi T; Eisinger F; Extra JM; Viens P; Jacquemier J; Sobol H

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer Genetics/CIC-P Inserm 9502, Paoli Calmettes Institute, University of Aix-Marseille II, Marseille, France.

**RESUMEN / SUMMARY:** - Family structure, lack of reliable information, cost, and delay are usual concerns when deciding to perform BRCA analyses. Testing breast cancer tissues with four antibodies (MS110, lys27H3, vimentin, and KI67) in addition to grade evaluation enabled us to rapidly select patients for genetic testing identification. We constituted an initial breast cancer tissue microarray, considered as a learning set, comprising 27 BRCA1 and 81 sporadic tumors. A second independent validation set of 28 BRCA1 tumors was matched to 28 sporadic tumors using the same original conditions. We investigated morphological parameters and 21 markers by immunohistochemistry. A logistic regression model was used to select the minimal number of markers providing the best model to predict BRCA1 status. The model was applied to the validation set to estimate specificity and sensibility. In the initial set, univariate analyses identified 11 markers significantly associated with BRCA1 status. Then, the best multivariate model comprised only grade 3, MS110, Lys27H3, vimentin, and KI67. When applied to the validation set, BRCA1 tumors were correctly classified with a sensitivity of 83% and a specificity of 81%. The performance of this model was superior when compared to other profiles. This study offers a new rapid and cost-effective method for the prescreening of patients at high risk of being BRCA1 mutation carriers, to guide genetic testing, and finally to provide appropriate preventive measures, advice, and treatments including targeted therapy to patients and their families.

[742]

**TÍTULO / TITLE:** - Role of mitogen-activated protein kinase cascades in 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced apoptosis in neuronal pheochromocytoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Exp Toxicol. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago)

[1177/0960327113482595](#)

**AUTORES / AUTHORS:** - Xu G; Duan Z; Chen G; Nie X; Liu J; Zhang Y; Li Y; Wan C; Jiang J

**INSTITUCIÓN / INSTITUTION:** - 1Department of Nutrition and Food Hygiene, School of Public Health, Nantong University, Nantong, Jiangsu, People's Republic of China.

**RESUMEN / SUMMARY:** - Mitogen-activated protein kinases (MAPKs) are involved in neuronal death caused by many cytotoxins. Conventional MAPKs consist of three family members: extracellular signal-regulated kinase-1/2 (ERK1/2), c-Jun N-terminal kinase (JNK) and p38. It has been originally shown that ERK1/2 is important for cell survival, whereas JNK and p38 are deemed stress responsive and thus involved in apoptosis. However, information describing the role of MAPKs in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced neurotoxicity is insufficient. The aim of this study was to identify the role of MAPK cascades in TCDD-induced neurotoxicity using differentiated pheochromocytoma (PC12) cells as a model for neuronal cells. Cell viability assay, terminal deoxynucleotidyl transferase dUTP nick-end labeling assay and flow cytometry analysis showed that TCDD attenuated cell viability with a dose- and time-dependent manner and significantly induced apoptosis in primary cortical neurons and PC12 cells. Western blot analysis indicated that TCDD markedly activated the expression of ERK1/2, JNK and p38 in TCDD-treated PC12 cells. Furthermore, PD98059 (ERK1/2 inhibitor), SP600125 (JNK inhibitor) and SB202190 (p38 inhibitor) notably blocked the effect of TCDD on cell apoptosis. Based on the findings above, it is concluded that the activation of MAPK signaling pathways may be associated with TCDD-mediated neuronal apoptosis.

[743]

**TÍTULO / TITLE:** - The role of intracrine androgen metabolism, androgen receptor and apoptosis in the survival and recurrence of prostate cancer during androgen deprivation therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Drug Targets. 2013 Apr;14(4):420-40.

**AUTORES / AUTHORS:** - Fiandalo MV; Wu W; Mohler JL

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.

**RESUMEN / SUMMARY:** - Prostate cancer (CaP) is the most frequently diagnosed cancer and leading cause of cancer death in American men. Almost all men present with advanced CaP and some men who fail potentially curative therapy are treated with androgen deprivation therapy (ADT). ADT is not curative and CaP recurs as the lethal phenotype. The goal of this review is to apply our current understanding of CaP and castration-recurrent CaP (CR-CaP) to earlier studies that characterized ADT and the molecular mechanisms that facilitate the transition from androgen-stimulated CaP to CR-CaP. Reexamination of earlier studies also may provide a better understanding of how more newly recognized mechanisms, such as intracrine metabolism, may be involved with the early events that allow CaP survival after initiation of ADT and subsequent development of CR-CaP.

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[744]

**TÍTULO / TITLE:** - Proteomic and cytokine plasma biomarkers for predicting progression from colorectal adenoma to carcinoma in human patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proteomics. 2013 Apr 20. doi: 10.1002/pmic.201200550.

●●Enlace al texto completo (gratis o de pago) [1002/pmic.201200550](#)

**AUTORES / AUTHORS:** - Choi JW; Liu H; Shin DH; Yu GI; Hwang JS; Kim ES; Yun JW

**INSTITUCIÓN / INSTITUTION:** - Department of Biotechnology, Daegu University, Kyungsan, Kyungbuk, 712-714, Republic of Korea.

**RESUMEN / SUMMARY:** - In the present study, we screened proteomic and cytokine biomarkers between patients with adenomatous polyps and colorectal cancer (CRC) in order to improve our understanding of the molecular mechanisms behind tumorigenesis and tumor progression in CRC. To this end, we performed comparative proteomic analysis of plasma proteins using a combination of 2-DE and mass spectrometry as well as profiled differentially regulated cytokines and chemokines by multiplex bead analysis. Proteomic analysis identified 11 up-regulated and 13 down-regulated plasma proteins showing significantly different regulation patterns with diagnostic potential for predicting progression from adenoma to carcinoma. Some of these proteins have not previously been implicated in CRC, including up-regulated leucine-rich alpha-2-glycoprotein, hemoglobin subunit beta, Ig alpha-2 chain C region, and complement factor B as well as down-regulated afamin, zinc-alpha-2-glycoprotein, vitronectin, and alpha1-antichymotrypsin. In addition, plasma levels of three cytokines/chemokines, including interleukin-8, interferon gamma-induced protein 10, and tumor necrosis factor alpha, were remarkably elevated in patients with CRC compared to those with adenomatous polyps. Although further clinical validation is required, these proteins and cytokines can be

established as novel biomarkers for CRC and/or its progression from colon adenoma. This article is protected by copyright. All rights reserved.

[745]

**TÍTULO / TITLE:** - Human epidermal growth factor receptor 2-targeted therapies in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Biol Ther. 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago)

[1517/14712598.2013.789497](#)

**AUTORES / AUTHORS:** - Nahta R

**INSTITUCIÓN / INSTITUTION:** - Emory University School of Medicine , Suite 5001, 1510 Clifton Road, Atlanta, GA 30322 , USA +1 404 778 3097 ; +1 404 778 5530 ; [rnahta@emory.edu](mailto:rnahta@emory.edu).

**RESUMEN / SUMMARY:** - Human epidermal growth factor receptor 2 (HER2) was acknowledged as an important therapeutic target in breast cancer more than 25 years ago. Subsequently, significant basic science and translational discoveries have resulted in the approval of four HER2-targeted therapies over the past 15 years. This editorial discusses future challenges regarding selection and development of treatments for HER2-positive breast cancer, which can only be met by continuing to support research efforts into the basic mechanisms by which cancer cells escape targeted therapies. Identifying specific molecular mechanisms underlying the sensitivity or resistance to each HER2-targeted agent will ultimately allow individualized therapy for each patient.

[746]

**TÍTULO / TITLE:** - Inhibition of the PI3K/AKT pathway potentiates cytotoxicity of EGFR kinase inhibitors in triple-negative breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Mol Med. 2013 May;17(5):648-56. doi: 10.1111/jcmm.12046. Epub 2013 Apr 20.

●●Enlace al texto completo (gratis o de pago) [1111/jcmm.12046](#)

**AUTORES / AUTHORS:** - Yi YW; Hong W; Kang HJ; Kim HJ; Zhao W; Wang A; Seong YS; Bae I

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; Department of Nanobiomedical Science and WCU (World Class University) Research Center of Nanobiomedical Science, Dankook University, Cheonan, Korea.

**RESUMEN / SUMMARY:** - Triple-negative breast cancers (TNBCs) are known to be intrinsically resistant to inhibitors for epidermal growth factor receptor (EGFR). Until now, clinical trials for TNBCs using EGFR inhibitors (EGFRis) as

single agents have yielded disappointing results. Here, we report that combinatorial treatment using EGFRis, such as gefitinib or erlotinib, with PI3K/AKT pathway inhibitors (PI3K/AKTis) demonstrated a synergistic, anti-proliferative effect in cell lines of the basal-like (BL) subtype, a subtype of TNBC. Western blot analysis revealed that the gefitinib/PI-103 combination significantly reduced the level of both phospho-AKT and phospho-ERK in two susceptible BL subtype cell lines, SUM149PT and MDA-MB-468, whereas it had little or no effect on the level of phospho-ERK in two non-susceptible cell lines (HS578T and MDA-MB-231) of mesenchymal stem-like (MSL) TNBC subtype. The gefitinib/PI-103 combination also significantly induced caspase-3/7-mediated PARP cleavage and reduced two anti-apoptotic proteins, XIAP and Bcl-2 in the susceptible cell lines. In addition, the level of myeloid cell leukemia 1 (Mcl-1) protein was markedly decreased by gefitinib/PI-103 combination in the BL TNBC cells, but showed no significant change by this combination in MSL subtype cells. These results suggest that pharmacological inhibition of EGFR used in combination of PI3K/AKTis is a potential therapeutic approach to treat a subtype of TNBCs.

[747]

**TÍTULO / TITLE:** - The novel BH3 alpha-helix mimetic JY-1-106 induces apoptosis in a subset of cancer cells (lung cancer, colon cancer and mesothelioma) by disrupting Bcl-xL and Mcl-1 protein-protein interactions with Bak.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer. 2013 May 16;12(1):42. doi: 10.1186/1476-4598-12-42.

●●Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-42](#)

**AUTORES / AUTHORS:** - Cao X; Yap JL; Newell-Rogers MK; Peddaboina C; Jiang W; Papaconstantinou HT; Jupiter D; Rai A; Jung KY; Tubin RP; Yu W; Vanommeslaeghe K; Wilder PT; Mackerell AD Jr; Fletcher S; Smythe RW

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Scott & White Memorial Hospital and Clinic, The Texas A&M University System, Health Science Center, College of Medicine, 702 SW HK Dodgen Loop, Temple, Texas 76504, USA. [rsmythe@sw.org](mailto:rsmythe@sw.org).

**RESUMEN / SUMMARY:** - BACKGROUND: It has been shown in many solid tumors that the overexpression of the pro-survival Bcl-2 family members Bcl-2/Bcl-xL and Mcl-1 confers resistance to a variety of chemotherapeutic agents. We designed the BH3 alpha-helix mimetic JY-1-106 to engage the hydrophobic BH3-binding grooves on the surfaces of both Bcl-xL and Mcl-1. METHODS: JY-1-106-protein complexes were studied using molecular dynamics (MD) simulations and the SILCS methodology. We have evaluated the in vitro effects of JY-1-106 by using a fluorescence polarization (FP) assay, an XTT assay, apoptosis assays, and immunoprecipitation and western-blot assays. A

preclinical human cancer xenograft model was used to test the efficacy of JY-1-106 in vivo. RESULTS: MD and SILCS simulations of the JY-1-106-protein complexes indicated the importance of the aliphatic side chains of JY-1-106 to binding and successfully predicted the improved affinity of the ligand for Bcl-xL over Mcl-1. Ligand binding affinities were measured via an FP assay using a fluorescently labeled Bak-BH3 peptide in vitro. Apoptosis induction via JY-1-106 was evidenced by TUNEL assay and PARP cleavage as well as by Bax-Bax dimerization. Release of multi-domain Bak from its inhibitory binding to Bcl-2/Bcl-xL and Mcl-1 using JY-1-106 was detected via immunoprecipitation (IP) western blotting. At the cellular level, we compared the growth proliferation IC50s of JY-1-106 and ABT-737 in multiple cancer cell lines with various Bcl-xL and Mcl-1 expression levels. JY-1-106 effectively induced cell death regardless of the Mcl-1 expression level in ABT-737 resistant solid tumor cells, whilst toxicity toward normal human endothelial cells was limited. Furthermore, synergistic effects were observed in A549 cells using a combination of JY-1-106 and multiple chemotherapeutic agents. We also observed that JY-1-106 was a very effective agent in inducing apoptosis in metabolically stressed tumors. Finally, JY-1-106 was evaluated in a tumor-bearing nude mouse model, and was found to effectively repress tumor growth. Strong TUNEL signals in the tumor cells demonstrated the effectiveness of JY-1-106 in this animal model. No significant side effects were observed in mouse organs after multiple injections. CONCLUSIONS: Taken together, these observations demonstrate that JY-1-106 is an effective pan-Bcl-2 inhibitor with very promising clinical potential.

[748]

**TÍTULO / TITLE:** - HER2-positive breast cancer patients receiving trastuzumab treatment obtain prognosis comparable with that of HER2-negative breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Onco Targets Ther. 2013 Apr 9;6:341-7. doi: 10.2147/OTT.S40851. Print 2013.

●●Enlace al texto completo (gratis o de pago) [2147/OTT.S40851](#)

**AUTORES / AUTHORS:** - Qin T; Yuan Z; Peng R; Bai B; Shi Y; Teng X; Liu D; Wang S

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: The efficacy of trastuzumab in Chinese breast cancer (BC) patients has rarely been reported. This study was designed to compare the clinical outcomes of HER2-positive BC patients receiving or not receiving trastuzumab treatment and HER2-negative BC patients. PATIENTS AND METHODS: This study involved three groups of patients. The first group was 115 human epidermal growth factor receptor 2 (HER2)-positive BC patients

treated with trastuzumab who were enrolled at Sun Yat-sen University Cancer Center between January 2002 and July 2010; the second group was a matched control group of 115 HER2-positive patients who did not receive trastuzumab treatment; the third group was a matched group of 115 HER2-negative patients who received conventional therapy in the adjuvant setting. The primary endpoint was 3-year and 5-year disease-free survival (3-DFS and 5-DFS, respectively). The Kaplan-Meier method, log-rank test, and multivariate Cox proportional hazard regression model were used for survival analysis. The differences in survival rates among the three groups were also analyzed according to two different periods: 2002-2006 and 2007-2010. RESULTS: The median duration of follow-up was 36 months (range, 12-111 months). The 3-DFS rates in the HER2-negative group, the HER2-positive group who received trastuzumab treatment, and the HER2-positive group who did not receive trastuzumab treatment were 82.6%, 89.6%, and 67.0%, respectively. The 3-DFS rate for the total study population was statistically significant ( $P < 0.001$ ). Further analysis indicated a statistically significant difference in 3-DFS between either of the first two groups and the third group ( $P < 0.01$ ), but the difference between the first two groups was not statistically significant ( $P = 0.157$ ). Among the three groups, the 3-DFS rates during 2002-2006 did not have a significant difference compared with that during 2007-2010. CONCLUSION: This study has further confirmed the efficacy of trastuzumab for HER2-positive operable BC in Chinese patients. It has also demonstrated that the 3-DFS and 5-DFS rates between HER2-positive patients receiving trastuzumab treatment and HER2-negative patients are comparable.

[749]

**TÍTULO / TITLE:** - Sustained EKR inhibition by EGFR targeting therapies is a predictive factor for synergistic cytotoxicity with PDT as neoadjuvant therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 Mar;1830(3):2659-70.

**AUTORES / AUTHORS:** - Weyergang A; Selbo PK; Berg K

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital Montebello, N-0310 Oslo, Norway. [anette.weyergang@rr-research.no](mailto:anette.weyergang@rr-research.no)

**RESUMEN / SUMMARY:** - BACKGROUND: Tyrosin kinase inhibitors (TKIs) and monoclonal antibodies aimed to target epidermal growth factor receptor (EGFR) have shown limited effect as monotherapies and drug resistance is a major limitation for therapeutic success. Adjuvant therapies to EGFR targeting therapeutics are therefore of high clinical relevance. METHODS: Three EGFR targeting drugs, Cetuximab, Erlotinib and Tyrphostin AG1478 were used in combination with photodynamic therapy (PDT) in two EGFR positive cell lines, A-431 epidermoid skin carcinoma and WiDr colorectal adenocarcinoma cells. The amphiphilic meso-tetraphenylporphine with 2 sulphonate groups on adjacent phenyl rings (TPPS(2a)) was utilized as a photosensitizer for PDT.

The cytotoxic outcome of the combined treatments was evaluated by cell counting and MTT. Cellular signalling was explored by Western blotting. RESULTS: PDT as neoadjuvant to Tyrphostin in A-431 cells as well as to Tyrphostin or Erlotinib in WiDr cells revealed synergistic cytotoxicity. In contrast, Erlotinib or Cetuximab combined with neoadjuvant PDT induced an antagonistic effect on cell survival of A-431 cells. Neoadjuvant PDT and EGFR targeting therapies induced a synergistic inhibition of ERK as well as synergistic cytotoxicity only when the EGFR targeting monotherapies caused a prolonged ERK inhibition. There were no correlation between EGFR inhibition by the EGFR targeting monotherapies or the combined therapies and the cytotoxic outcome combination-therapies. CONCLUSIONS: The results suggest that sustained ERK inhibition by EGFR targeting monotherapies is a predictive factor for synergistic cytotoxicity when combined with neoadjuvant PDT. GENERAL SIGNIFICANCE: The present study provides a rationale for selecting anticancer drugs which may benefit from PDT as adjuvant therapy.

[750]

**TÍTULO / TITLE:** - High EGFR copy number predicts benefits from tyrosine kinase inhibitor treatment for non-small cell lung cancer patients with wild-type EGFR.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 Apr 4;11(1):90.

●●Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-90](#)

**AUTORES / AUTHORS:** - Wang F; Fu S; Shao Q; Zhou YB; Zhang X; Zhang X; Xue C; Lin JG; Huang LX; Zhang L; Zhang WM; Shao JY

**RESUMEN / SUMMARY:** - BACKGROUND: This study was designed to determine whether advanced non-small-cell lung cancer (NSCLC) patients with high copy number of epidermal growth factor receptor (EGFR) can benefit from treatment with EGFR-tyrosine kinase inhibitors (TKIs). METHODS: EGFR gene copy number was assessed by fluorescence in situ hybridization (FISH) and EGFR mutations was tested using Luminex xTAG technology in 502 TKI-treated NSCLC patients. The association between both biomarkers and clinical benefit from EGFR-TKI were analyzed. RESULTS: EGFR FISH + and EGFR mutations were significantly associated with higher response rates (37.2% and 43.7%, respectively), superior progression-free survival (PFS) (FISH+, 11.2 months; hazard ratio [HR], 0.51; 95% CI, 0.42 to 0.62;  $p < 0.001$ ; mutation+, 11.7 months; HR, 0.37; 95% CI, 0.31 to 0.45;  $p < 0.001$ ) and overall survival (OS) (FISH+, 30.2 months; HR, 0.51; 95% CI, 0.40 to 0.65;  $p < 0.001$ ; mutation+, 30.2 months; HR, 0.45; 95% CI, 0.36 to 0.58;  $p < 0.001$ ). In patients with wild-type EGFR, EGFR FISH + correlated with longer PFS than EGFR FISH- status (4.4 months vs. 2.0 months; HR, 0.56; 95% CI, 0.41 to 0.75;  $p < 0.001$ ), so did amplification (5.0 months vs. 2.0 months; HR, 0.43; 95% CI, 0.24 to 0.76;  $p = 0.003$ ). However, FISH + had no association with improved PFS in EGFR-mutated patients (HR, 0.77; 95% CI, 0.57 to 1.03;  $p = 0.076$ ). CONCLUSIONS:

A combined analysis of EGFR FISH and mutation is an effective predictor of EGFR-TKI therapy. Specifically, a high EGFR copy number may predict benefit from TKIs treatment for NSCLC patients with wild-type EGFR.

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[751]

**TÍTULO / TITLE:** - Oncogenic Variant RON160 Expression in Breast Cancer and its Potential as a Therapeutic Target by Small Molecule Tyrosine Kinase Inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Cancer Drug Targets. 2013 Apr 17.

**AUTORES / AUTHORS:** - Yao HP; Zhuang CM; Zhou YQ; Zeng JY; Zhang RW; Wang MH

**INSTITUCIÓN / INSTITUTION:** - Department of Biomedical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, 1406 S. Coulter Street, Amarillo, TX 79106, USA. [minghai.wang@ttuhsc.edu](mailto:minghai.wang@ttuhsc.edu).

**RESUMEN / SUMMARY:** - Aberrant expression of the RON receptor tyrosine kinase contributes to breast cancer malignancy. Although clinical trials of RON targeting are underway, the intriguing issue is the diversity of RON expression as evident by cancer cells expressing different variants including oncogenic RON160. The current study determines aberrant RON160 expression in breast cancer and its potential as a target for breast cancer therapy. Using mouse monoclonal antibody Zt/h12 in immunohistochemical staining of breast cancer tissue microarray, we observed that RON160 was expressed in high frequency in primary invasive ductal (77.2%, 61/79 cases), lobular (42.5%, 34/80 cases), and lymph node-involved (63.9%, 26/36 cases) breast cancer samples. Moreover, RON160 overexpression was predominantly observed in invasive ductal (26.6%, 21/79 cases) and lymph node-involved (33.3%, 12/36) cases. Among a panel of breast cancer cell lines analyzed, Du4475 cells naturally expressing RON160. Silencing RON160 expression by siRNA reduces Du4475 cell viability. Inhibition of RON160 signaling by tyrosine kinase inhibitor PHA665752 also suppressed Du4475 cell anchorage-independent growth and induced apoptotic cell death. Studies in vivo revealed that PHA665752 inhibited 3T3-RON160 and Du4475 cell-mediated tumor growth in mouse mammary fat pad. A 60% reduction in tumor volume compared to controls was achieved after a 13-day treatment. We conclude from these studies that RON160 is highly expressed in breast cancer and its signaling is integrated into cellular signaling network for tumor cell growth and survival. Experimental treatment by PHA665752 in Du4475 breast cancer xenograft model highlights the significance of RON160 as a drug target in molecular-targeted breast cancer therapy.

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[752]

**TÍTULO / TITLE:** - Aurora B inhibitor barasertib and cytarabine exert a greater-than-additive cytotoxicity in acute myeloid leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Apr 4. doi: 10.1111/cas.12164.

●●Enlace al texto completo (gratis o de pago) [1111/cas.12164](#)

**AUTORES / AUTHORS:** - Yamauchi T; Uzui K; Shigemi H; Negoro E; Yoshida A; Ueda T

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Oncology, University of Fukui, Fukui, Japan.

**RESUMEN / SUMMARY:** - Barasertib, an aurora B inhibitor, terminates cell division, introduces polyploidy, and consequently causes apoptosis. In the present study, we evaluated the effect of the combination of barasertib and cytarabine (ara-C), a key agent for leukemia chemotherapy, on leukemic cells in vitro. Human leukemia HL-60 cells and HL-60/ara-C20 cells, a 20-fold ara-C-resistant variant, were used. The 50% growth inhibitory concentrations of an active metabolite of barasertib, barasertib-hydroxyquinazoline-pyrazol-aniline (Barasertib-HQPA), and ara-C were 51 nM and 300 nM for HL-60 cells and 70 nM and 5300 nM for HL-60/ara-C20 cells, respectively. Barasertib-HQPA induced polyploidy with a subsequent induction of sub-G1 phase apoptosis, indicating the M-phase specific cytotoxicity. Cells treated with the S-phase specific ara-C accumulated in S phase and subsequently died through apoptosis. When HL-60 cells were treated with barasertib-HQPA and ara-C in combination, a greater-than-additive apoptosis was induced. This enhancement was obtained when the cells were treated with barasertib-HQPA prior to ara-C (37.9% sub-G1) or with both concurrently (31.2% sub-G1), but not with ara-C prior to barasertib-HQPA (17.8% sub-G1). The combination effects were similarly obtained in HL-60/ara-C20 cells with 19.7% sub-G1 for barasertib-HQPA-->ara-C, 18.4% sub-G1 for both concurrently, and 13.8% sub-G1 for ara-C-->barasertib-HQPA, and another leukemic U937 cells with 25.4% sub-G1 for barasertib-HQPA-->ara-C, 28.2% sub-G1 for both concurrently, and 16.0% sub-G1 for ara-C-->barasertib-HQPA. Barasertib-HQPA inhibited aurora B autophosphorylation and histone H3 phosphorylation in all the cell lines. Barasertib-HQPA did not inhibit DNA synthesis, allowing ara-C incorporation into DNA for its cytotoxicity. Thus, barasertib-HQPA and ara-C provided a greater-than-additive cytotoxicity in leukemic cells in vitro.

[753]

**TÍTULO / TITLE:** - Targeting the Vav3 oncogene enhances docetaxel-induced apoptosis through the inhibition of androgen receptor phosphorylation in LNCaP prostate cancer cells under chronic hypoxia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer. 2013 Apr 8;12:27. doi: 10.1186/1476-4598-12-27.

●●Enlace al texto completo (gratuito o de pago) [1186/1476-4598-12-27](#)

**AUTORES / AUTHORS:** - Nomura T; Yamasaki M; Hirai K; Inoue T; Sato R; Matsuura K; Moriyama M; Sato F; Mimata H

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita 879-5593, Japan.

[TAKE@oita-u.ac.jp](mailto:TAKE@oita-u.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The Vav family of Rho/Rac guanosine nucleotide exchange factors comprises three members in mammalian cells. Vav3 enhances androgen receptor (AR) activity during progression to androgen independence in prostate cancer. We examined Vav3 small interfering RNA (siRNA) effects on cell proliferation and apoptosis in docetaxel-treated LNCaP cells under chronic hypoxia (LNCaPH). METHODS: We examined individual and combined effects of Vav3 siRNA (si-Vav3) and docetaxel on cell growth and apoptosis under chronic hypoxia by cell proliferation, flow cytometric, DNA fragmentation, and immunoblot analyses. To clarify the molecular basis of si-Vav3- and docetaxel-induced apoptosis, we analyzed alterations in phosphatidylinositol 3-kinase (PI3K)/Akt, extracellular signal-regulate kinase (ERK), c-jun N-terminal kinase (JNK), and AR pathways using kinase inhibitors in LNCaPH cells. The effects of si-Vav3/atelocollagen complex alone or in combination with docetaxel were assessed on xenografts in nude mice by tumor growth delay. RESULTS: Vav3 overexpression was observed in LNCaPH compared with the expression under normoxia. Interrupting Vav3 signaling using siRNA enhanced docetaxel-induced cell growth suppression compared with that induced by docetaxel alone by inhibition of Akt and ERK phosphorylation, resulting in AR phosphorylation inhibition. In addition to increased B-cell lymphoma 2 (Bcl-2) phosphorylation through JNK signaling in response to docetaxel, si-Vav3 enhanced docetaxel-induced apoptosis, as characterized by the accumulation of sub-G1 phase cells and DNA fragmentation, through Bcl-xL/Bcl-2-associated death promoter (Bad) dephosphorylation, resulting in increased caspase-9, caspase-3, and cleaved poly(ADP-ribose) polymerase activation. Xenograft tumor growth was slightly inhibited by si-Vav3/atelocollagen complex injection and combined use of si-Vav3/atelocollagen complex and docetaxel produced a greater effect than docetaxel alone. CONCLUSIONS: Interrupting Vav3 signaling enhances docetaxel-induced apoptosis in LNCaP cells under chronic hypoxia by inhibiting the PI3K/Akt, ERK, and AR signaling pathways. Therapy targeting Vav3 in combination with docetaxel may have practical implications for managing castration-resistant prostate cancer.

[754]

**TÍTULO / TITLE:** - Phospholipid Scramblase 1, an interferon-regulated gene located at 3q23, is regulated by SnoN/SkiL in ovarian cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer. 2013 Apr 26;12:32. doi: 10.1186/1476-4598-12-32.

●●Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-32](https://doi.org/10.1186/1476-4598-12-32)

**AUTORES / AUTHORS:** - Kodigepalli KM; Anur P; Spellman P; Sims PJ; Nanjundan M

**INSTITUCIÓN / INSTITUTION:** - Department of Cell Biology, Microbiology, and Molecular Biology, University of South Florida, 4202 East Fowler Avenue, ISA2015, Tampa, FL 33620, USA. [mnanjund@usf.edu](mailto:mnanjund@usf.edu).

**RESUMEN / SUMMARY:** - BACKGROUND: Treatment of advanced stage ovarian cancer continues to be challenging due to acquired drug resistance and lack of early stage biomarkers. Genes identified to be aberrantly expressed at the 3q26.2 locus (i.e. SnoN/SkiL) have been implicated in ovarian cancer pathophysiology. We have previously shown that SnoN expression is increased in advanced stage ovarian cancers and alters cellular response to arsenic trioxide (As<sub>2</sub>O<sub>3</sub>). FINDINGS: We now demonstrate increased DNA copy number levels (TCGA data) of phospholipid scramblase 1 (PLSCR1, located at 3q23) whose transcript expression in ovarian cell lines is highly correlated with SnoN mRNA. Interestingly, SnoN can modulate PLSCR1 mRNA levels in the absence/presence of interferon (IFN-2alpha). Both IFN-2alpha and As<sub>2</sub>O<sub>3</sub> treatment can modulate PLSCR1 mRNA levels in ovarian carcinoma cells. However, SnoN siRNA does not lead to altered PLSCR1 protein implicating other events needed to modulate its protein levels. In addition, we report that PLSCR1 can modulate aspects of the As<sub>2</sub>O<sub>3</sub> cellular response. CONCLUSIONS: Our findings warrant further investigation into the role of PLSCR1 in ovarian cancer development and chemoresistance.

[755]

**TÍTULO / TITLE:** - Prognostic Role of Human Epidermal Growth Factor Receptor 2 Status in Premenopausal Early Breast Cancer Treated With Adjuvant Tamoxifen.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Breast Cancer. 2013 May 14. pii: S1526-8209(13)00050-5. doi: 10.1016/j.clbc.2013.02.005.

●●Enlace al texto completo (gratis o de pago) [1016/j.clbc.2013.02.005](https://doi.org/10.1016/j.clbc.2013.02.005)

**AUTORES / AUTHORS:** - Meattini I; Livi L; Saieva C; Franceschini D; Scotti V; Mangoni M; Loi M; Brina LD; Zei G; Bonomo P; Greto D; Gelain E; Nori J; Sanchez LJ; Orzalesi L; Bianchi S; Biti G

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation-Oncology, University of Florence, Florence, Italy. Electronic address: [icro.meattini@unifi.it](mailto:icro.meattini@unifi.it).

**RESUMEN / SUMMARY:** - BACKGROUND: Hormone therapy is the most prescribed systemic therapy for patients with breast cancer (BC). Some patients fail to respond to tamoxifen; one pathway seems to involve human epidermal growth factor receptor 2 (HER2) overexpression. To better

understand this matter, we reviewed our single-center experience of premenopausal patients who were chemotherapy naive and treated with 5 years of tamoxifen for early-stage BC by focusing on estrogen receptor (ER), progesterone receptor, HER2 status, and Ki-67 proliferative index. PATIENTS AND METHODS: We reviewed 425 patients treated with tamoxifen for early-stage BC. Previous solid tumors, age less than 18 years, BC recurrences or contralateral tumor, tamoxifen discontinuation, adjuvant chemotherapy, and a follow-up shorter than 6 months were considered exclusions criteria of the study. RESULTS: At a mean follow-up of 8.1 years, the mean (SD) time to local relapse was 6.7 +/- 3.6 years; range, 2.0-10.7 years), whereas the mean (SD) time to distant metastases was 4.7 +/- 2.3 years; range, 2.2-8.8 years). HER2 status did not influence local relapse-free survival (log-rank test, 0.40), distant metastases-free survival (log-rank test, 0.72), and overall survival rate (log-rank test, 0.87). CONCLUSIONS: Resistance to tamoxifen is a complex trait, and its pathway is still unclear; in patients with BC, a multidisciplinary approach is highly recommended. In our experience, we did not find a statistically significant difference in tamoxifen treatment efficacy according to HER2 status.

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[756]

**TÍTULO / TITLE:** - Resident rounds. Part III: Neutrophilic eccrine hidradenitis in the setting of acute myelogenous leukemia treated with cytarabine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Drugs Dermatol. 2013 Feb;12(2):231-2.

**AUTORES / AUTHORS:** - Shlapak D; Kerisit K; Lin C; Wang A; Stumpf B

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, Tulane University School of Medicine, New Orleans, LA, USA.

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[757]

**TÍTULO / TITLE:** - Identification of a lung adenocarcinoma cell line with CCDC6-RET fusion gene and the effect of RET inhibitors in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Apr 11. doi: 10.1111/cas.12175.

●●Enlace al texto completo (gratis o de pago) [1111/cas.12175](#)

**AUTORES / AUTHORS:** - Suzuki M; Makinoshima H; Matsumoto S; Suzuki A; Mimaki S; Matsushima K; Yoh K; Goto K; Suzuki Y; Ishii G; Ochiai A; Tsuta K; Shibata T; Kohno T; Esumi H; Tsuchihara K

**INSTITUCIÓN / INSTITUTION:** - Division of Translational Research, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Kashiwa, Chiba, Japan.

**RESUMEN / SUMMARY:** - Rearrangements of the proto-oncogene RET are newly identified potential driver mutations in lung adenocarcinoma (LAD). However,

the absence of cell lines harboring RET fusion genes has hampered the investigation of the biological relevance of RET and the development of RET-targeted therapy. Thus, we aimed to identify a RET fusion positive LAD cell line. Eleven LAD cell lines were screened for RET fusion transcripts by reverse transcription-polymerase chain reaction. The biological relevance of the CCDC6-RET gene products was assessed by cell growth, survival and phosphorylation of ERK1/2 and AKT with or without the suppression of RET expression using RNA interference. The efficacy of RET inhibitors was evaluated in vitro using a culture system and in an in vivo xenograft model. Expression of the CCDC6-RET fusion gene in LC-2/ad cells was demonstrated by the mRNA and protein levels, and the genomic break-point was confirmed by genomic DNA sequencing. Mutations in KRAS and EGFR were not observed in the LC-2/ad cells. CCDC6-RET was constitutively active, and the introduction of a siRNA targeting the RET 3' region decreased cell proliferation by downregulating RET and ERK1/2 phosphorylation. Moreover, treatment with RET-inhibitors, including vandetanib, reduced cell viability, which was accompanied by the downregulation of the AKT and ERK1/2 signaling pathways. Vandetanib exhibited anti-tumor effects in the xenograft model. Endogenously expressing CCDC6-RET contributed to cell growth. The inhibition of kinase activity could be an effective treatment strategy for LAD. LC-2/ad is a useful model for developing fusion RET-targeted therapy.

[758]

**TÍTULO / TITLE:** - Protein kinase D1 mRNA level may predict cancer-specific survival in heavy smokers with esophageal squamous cell cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dis Esophagus. 2013 Apr 26. doi: 10.1111/dote.12077.

●●Enlace al texto completo (gratis o de pago) [1111/dote.12077](#)

**AUTORES / AUTHORS:** - Xie X; Zhang SS; Wen J; Yang H; Luo KJ; Yang F; Hu Y; Fu JH

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in South China, Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangdong Esophageal Cancer Research Institute, Guangzhou, China.

**RESUMEN / SUMMARY:** - Protein kinase D1 (PRKD1) is a kinase that regulates various pathways, which involve in cell proliferation, apoptosis, cell adhesion and invasion. Although PRKD1 expression has been observed in many cancers, its role in esophageal squamous cell cancer (ESCC) has not been well reported. As its dysregulation in cancers is organ specific, we sought to investigate the potential role of PRKD1 in the progression of ESCC. Samples were collected from 178 patients with completely resected ESCCs at Sun Yat-sen University Cancer Center, including 47 pairs of tumorous and non-tumorous tissues. PRKD1 mRNA expression was investigated by quantitative real-time polymerase chain reaction. Receiver operating characteristic (ROC) curve

analysis was used to search for a feasible cut-off point of PRKD1 mRNA levels for predicting cancer-specific survival. Kaplan-Meier and multivariate Cox regression analysis were used to assess the prognostic value of PRKD1 mRNA level in ESCC patients. In result, upregulation of PRKD1 mRNA was detected in 55.3% (26/47) of ESCC tissues compared with paired non-tumorous ones (P = 0.011). ROC analysis indicated 3.28 as a cut-off point, and thus 72 and 106 tumors with low and high PRKD1 mRNA expression were categorized. High-PRKD1 mRNA expression in tumors appeared with more frequency in heavy smokers (P = 0.002) and patients with advanced pathological T category (P = 0.034). Kaplan-Meier analysis indicated that patients with low-PRKD1 mRNA had a longer cancer-specific survival than the ones with high-PRKD1 level (P = 0.044). Multivariate analysis showed that tumorous PRKD1 mRNA expression was an independent prognostic factor (hazard ratio: 1.538, 95% confidence interval: 1.018-2.323, P = 0.041) in resected ESCC. Subgroup analysis revealed that the discernibility of PRKD1 mRNA level on ESCC outcomes was only pronounced in heavy smokers (P = 0.002), but not in non-heavy smokers (P = 0.870). PRKD1 might play a potential oncogenic role in ESCC. It might be an independent biomarker to predict prognosis in heavy smokers with ESCC.

[759]

**TÍTULO / TITLE:** - Plasma proteins interaction with curcumin nanoparticles: implications in cancer therapeutics.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Drug Metab. 2013 May 1;14(4):504-15.

**AUTORES / AUTHORS:** - Yallapu MM; Ebeling MC; Jaggi M; Chauhan SC

**INSTITUCIÓN / INSTITUTION:** - Cancer Biology Research Center, Sanford Research/University of South Dakota, 2301 E. 60<sup>th</sup> Street North, Sioux Falls, SD 57104-0589, USA. [Subhash.Chaohan@sanfordhealth.org](mailto:Subhash.Chaohan@sanfordhealth.org).

**RESUMEN / SUMMARY:** - Curcumin, a natural bioactive polyphenol, has been widely investigated as a conventional medicine for centuries. Over the past two decades, major pre-clinical and clinical trials have demonstrated its safe therapeutic profile but clinical translation has been hampered due to rapid degradation, poor water solubility, bioavailability and pharmaco-kinetics. To overcome such translational issues, many laboratories have focused on developing curcumin nanoformulations for cancer therapeutics. In this review, we discuss the evolution of curcumin nanomedicine in cancer therapeutics, the possible interactions between the surface of curcumin nanoparticles and plasma proteins, the role of nanoparticle-protein complex architecture parameters, and the rational design of clinically useful curcumin nanoformulations. Considering all the biologically relevant phenomena, curcumin nanoformulations can be developed as a new nutraceutical or pharmaceutical agent.

[760]

**TÍTULO / TITLE:** - IGF-1R targeting increases the antitumor effects of DNA damaging agents in SCLC model: an opportunity to increase the efficacy of standard therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 2.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1067](#)

**AUTORES / AUTHORS:** - Ferte C; Loriot Y; Clemenson C; Commo F; Gombos A; Bibault JE; Fumagalli I; Hamama S; Auger N; Lahon B; Chargari C; Calderaro J; Soria JC; Deutsch E

**INSTITUCIÓN / INSTITUTION:** - IINSERM U1030, Paris XI University, Institut Gustave Roussy.

**RESUMEN / SUMMARY:** - Insulin-like growth factor receptor-1 (IGF-1R) inhibition could be a relevant therapeutic approach in small cell lung cancer (SCLC) given the importance of an IGF-1R autocrine loop and its role in DNA damage repair processes. We assessed IGF-1R and pAkt protein expression in 83 SCLC human specimens. The efficacy of R1507 (a monoclonal antibody directed against IGF-1R) alone or combined with cisplatin or ionizing radiation (IR) was evaluated in H69, H146 and H526 cells in vitro and in vivo. Innovative genomic and functional approaches were conducted to analyze the molecular behavior under the different treatment conditions. A total of 53% and 37% of human specimens expressed IGF-1R and pAkt, respectively. R1507 demonstrated single agent activity in H146 and H526 cells but not in H69 cells. R1507 exhibited synergistic effects with both Cisplatin and IR in vitro. The triple combination R1507-Cisplatin-IR led to a dramatic delay in tumor growth compared to Cisplatin-IR in H526 cells. Analyzing the apparent absence of antitumoral effect of R1507 alone in vivo, we observed a transient reduction of IGF-1R staining intensity in vivo, concomitant to the activation of multiple cell surface receptors and intracellular proteins involved in proliferation, angiogenesis and survival. Finally, we identified that the nucleotide excision repair pathway (NER) was mediated after exposure to R1507-CDDP and R1507-IR in vitro and in vivo. In conclusion, adding R1507 to the current standard Cisplatin-IR doublet reveals remarkable chemo- and radiosensitizing effects in selected SCLC models and warrants to be investigated in the clinical setting.

[761]

**TÍTULO / TITLE:** - Impact of metabolizing enzymes on drug response of endocrine therapy in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Rev Mol Diagn. 2013 May;13(4):349-65. doi: 10.1586/erm.13.26.

●●Enlace al texto completo (gratis o de pago) [1586/erm.13.26](https://doi.org/10.1586/erm.13.26)

**AUTORES / AUTHORS:** - Saladores PH; Precht JC; Schroth W; Brauch H; Schwab M

**INSTITUCIÓN / INSTITUTION:** - Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology and University of Tübingen, Auerbachstr. 112, 70376 Stuttgart, Germany.

**RESUMEN / SUMMARY:** - Estrogen-receptor positive breast cancer accounts for 75% of diagnosed breast cancers worldwide. There are currently two major options for adjuvant treatment: tamoxifen and aromatase inhibitors. Variability in metabolizing enzymes determines their pharmacokinetic profile, possibly affecting treatment response. Therefore, prediction of therapy outcome based on genotypes would enable a more personalized medicine approach, providing optimal therapy for each patient. In this review, the authors will discuss the current evidence on the most important metabolizing enzymes in endocrine therapy, with a special focus on CYP2D6 and its role in tamoxifen metabolism.

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[762]

**TÍTULO / TITLE:** - Higher rate of skin rash in a phase II trial with weekly nanoparticle albumin-bound paclitaxel and cisplatin combination in Chinese breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 9;13(1):232.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-232](https://doi.org/10.1186/1471-2407-13-232)

**AUTORES / AUTHORS:** - Tang LC; Wang BY; Sun S; Zhang J; Jia Z; Lu YH; Di GH; Shao ZM; Hu XC

**RESUMEN / SUMMARY:** - **PURPOSE** The aim of this phase II study is to explore the incidence of skin rash among advanced breast cancer(ABC) patients treated with weekly nab-paclitaxel and cisplatin combination. **METHOD:** S Nab-paclitaxel(125 mg/m<sup>2</sup>) was administered on days 1, 8, 15, followed by cisplatin(75 mg/m<sup>2</sup>) on day 1 every 28 day cycle until disease progression, intolerable toxicities or the maximum of 6 cycles. Patients who received a least one injection of the study drug were included in this analysis of the incidence of skin rash among Chinese patients. Toxicity was graded using the CTCAE4.0. Statistical analysis was carried out by using SPSS 16.0 (SPSS Inc, Chicago, IL). **RESULTS:** Seventy-three patients enrolled were qualified to be analyzed, and a total of 384 cycles were administered before the data first collected at Oct 1<sup>st</sup>, 2011. Rash was presented in 27 patients (37.0%). The most common sites involved were face (14/27), neck (14/27), limbs (18/27) and frictional parts of the trunk (10/27). Macular and papular rash with pruritus commonly occurred 2 (1-7) days after the first day of chemotherapy. Only one patient developed Grade 3 skin toxicity with generalized erythroderma and disfigurement of the

face requiring dose reduction. The rash gradually regressed 2 (1-10) days after antihistamines using and pigmentation remained in 13/27 cases. The incidence rate of skin rash was significantly different between Chinese and western patients ( $P < 0.0001$ ). CONCLUSION: A higher rate of maculo-papular rash occurred in Chinese breast cancer patients treated with weekly nab-paclitaxel comparing to western patients. The albumin component of nab-paclitaxel might be the cause of the skin disorder.

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[763]

**TÍTULO / TITLE:** - Collagen Triple Helix Repeat Containing-1 (CTHRC1) Expression in Invasive Ductal Carcinoma of the Breast: The Impact on Prognosis and Correlation to Clinicopathologic Features.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1007/s12253-013-9636-](#)

[y](#)

**AUTORES / AUTHORS:** - Kim JH; Baek TH; Yim HS; Kim KH; Jeong SH; Kang HB; Oh SS; Lee HG; Kim JW; Kim KD

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Eulji University School of Medicine, Daejeon, 301-070, Republic of Korea.

**RESUMEN / SUMMARY:** - CTHRC1 has been known as a regulator of collagen expression and cell migration. The aim of this research was to clarify the clinicopathologic significance of CTHRC1 expression in human breast cancer. 22 cases of breast cancer tissues, randomly selected from clinically diagnosed patients, showed a significant increase of CTHRC1 mRNA expression compared to the normal tissue from the same patients using RT-PCR and real-time PCR. Additionally we investigated breast cancers from 189 patients by immunohistochemistry (IHC). A high level of CTHRC1 expression was observed in 111 (58.7 %) out of 189 breast cancer patients and the expression was significantly correlated with histologic grade ( $P = 0.026$ ), nodal status ( $P < 0.001$ ), and TNM pathologic stage ( $P = 0.002$ ). High CTHRC1 expression was associated with a shorter recurrence free survival ( $P = 0.008$ ). Taken together, the results showed that CTHRC1 over-expression was significantly associated with clinicopathological factors of poor prognosis in invasive ductal carcinoma. CTHRC1 could be used as a supplementary prognostic biomarker and a potential therapeutic target in breast cancer.

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[764]

**TÍTULO / TITLE:** - Thiopurine s-methyltransferase pharmacogenetics in childhood acute lymphoblastic leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2013;999:273-84. doi: 10.1007/978-1-62703-357-2\_20.

●●Enlace al texto completo (gratis o de pago) [1007/978-1-62703-357-2\\_20](https://doi.org/10.1007/978-1-62703-357-2_20)

**AUTORES / AUTHORS:** - Yang JJ; Bhojwani D

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA.

**RESUMEN / SUMMARY:** - Pharmacogenetics is the growing field of study of genetic variations underlying interindividual differences in drug response. Inherited polymorphisms in genes coding for drug-metabolizing enzymes, transporters, and targets influence toxicity as well as efficacy associated with the medication. Thiopurines are agents widely used in hematologic malignancies, transplantation, and chronic inflammatory conditions. Myelosuppression is the commonly encountered dose-limiting toxicity. Polymorphisms in the thiopurine S-methyltransferase gene (TPMT), the predominant inactivating enzyme for thiopurines in hematopoietic tissue, are correlated with enzymatic activity of TPMT, thiopurine metabolism, and risk of clinical toxicity. In this chapter, we present TPMT genotype assessment that allows for prescribing pharmacogenetically guided doses to enhance patient safety and drug efficacy.

[765]

**TÍTULO / TITLE:** - Src mediates cigarette smoke-induced resistance to tyrosine kinase inhibitors in NSCLC cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1029](https://doi.org/10.1158/1535-7163.MCT-12-1029)

**AUTORES / AUTHORS:** - Filosto S; Baston DS; Chung S; Becker CR; Goldkorn T

**INSTITUCIÓN / INSTITUTION:** - 1Internal Medicine, UC Davis School of Medicine.

**RESUMEN / SUMMARY:** - The EGF Receptor (EGFR) is a proto-oncogene commonly dysregulated in several cancers including non-small cell lung cancer (NSCLC) and, thus, is targeted for treatment using tyrosine kinase inhibitors (TKIs) such as Erlotinib. However, despite the efficacy observed in NSCLC patients harboring oncogenic variants of the EGFR, general ineffectiveness of TKIs in NSCLC patients who are current and former smokers necessitates identification of novel mechanisms to overcome this phenomenon. Previously, we showed that NSCLC cells harboring either wild-type (WT) EGFR or oncogenic mutant (MT) L858R EGFR become resistant to the effects of TKIs when exposed to cigarette smoke (CS), evidenced by their auto-phosphorylation and prolonged downstream signaling. Here, we present Src as a target mediating CS-induced resistance to TKIs in both WT EGFR and L858R MT EGFR expressing NSCLC cells. First, we show that CS exposure of A549 cells leads to time-dependent activation of Src which then abnormally binds to the WT EGFR causing TKI resistance, contrasting previous observations of

constitutive binding between inactive Src and TKI-sensitive L858R MT EGFR. Next, we demonstrate that Src inhibition restores TKI sensitivity in CS-exposed NSCLC cells, preventing EGFR auto-phosphorylation in the presence of Erlotinib. Furthermore, we show that over-expression of a dominant-negative Src (Y527F/K295R) restores TKI sensitivity to A549 exposed to CS. Importantly, the TKI resistance that emerges even in CS-exposed L858R EGFR expressing NSCLC cells could be eliminated with Src inhibition. Together, these findings offer new rationale for using Src inhibitors for treating TKI-resistant NSCLC commonly observed in smokers.

[766]

**TÍTULO / TITLE:** - Metabolomics identifies pyrimidine starvation as the mechanism of 5-aminoimidazole-4-carboxamide-1-beta-ribose (AICAr) induced apoptosis in multiple myeloma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1042](#)

**AUTORES / AUTHORS:** - Bardeleben C; Sharma S; Reeve JR Jr; Bassilian S; Frost PJ; Hoang B; Shi Y; Lichtenstein A

**INSTITUCIÓN / INSTITUTION:** - 1Hematology, West LA VA/UCLA Medical Center.

**RESUMEN / SUMMARY:** - To investigate the mechanism by which AICAr induces apoptosis in multiple myeloma (MM) cells, we performed an unbiased metabolomics screen. AICAr had selective effects on nucleotide metabolism, resulting in an increase in purine metabolites and a decrease in pyrimidine metabolites. The most striking abnormality was a 26 x fold increase in orotate associated with a decrease in UMP levels, indicating an inhibition of UMP synthetase (UMPS), the last enzyme in the de novo pyrimidine biosynthetic pathway, which produces UMP from orotate and PRPP. As all pyrimidine nucleotides can be synthesized from UMP, this suggested the decrease in UMP would lead to pyrimidine starvation as a possible cause of AICAr-induced apoptosis. Exogenous pyrimidines uridine, cytidine and thymidine, but not purines adenosine or guanosine, rescued MM cells from AICAr-induced apoptosis, supporting this notion. In contrast, exogenous uridine had no protective effect on apoptosis resulting from bortezomib, melphalan or metformin. Rescue resulting from thymidine add-back indicated apoptosis was induced by limiting DNA synthesis rather than RNA synthesis. DNA replicative stress was identified by associated H2A.X phosphorylation in AICAr-treated cells, which was also prevented by uridine add-back. Although phosphorylation of AICAr by adenosine kinase was required to induce MM cell death, apoptosis was not associated with AMP-activated kinase activation or mTORC1 inhibition. A possible explanation for inhibition of UMP synthase activity by AICAr was a depression in cellular levels of PRPP, a substrate of UMP synthase. These data

identify pyrimidine biosynthesis as a potential molecular target for future therapeutics in MM cells.

[767]

**TÍTULO / TITLE:** - Molecular interactions of ErbB1 (EGFR) and integrin-beta1 in astrocytoma frozen sections predict clinical outcome and correlate with Akt-mediated in vitro radioresistance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neuro Oncol. 2013 Apr 17.

●●Enlace al texto completo (gratis o de pago) [1093/neuonc/not046](#)

**AUTORES / AUTHORS:** - Petras M; Lajtos T; Friedlander E; Klekner A; Pintye E; Feuerstein BG; Szollosi J; Vereb G

**INSTITUCIÓN / INSTITUTION:** - Department of Biophysics and Cell Biology (M.P., T.L., E.F., J.S., G.V.); Department of Neurosurgery (A.K.); Department of Radiotherapy (E.P.); MTA Cell Biology and Signaling Research Group (J.S., G.V.), Medical and Health Science Center, University of Debrecen, Debrecen, Hungary; and Department of Neurology, Barrow Neurological Institute-St. Joseph's Hospital and Medical Center, University of Arizona College of Medicine, Phoenix, Arizona (B.G.F.).

**RESUMEN / SUMMARY:** - Introduction Treatment of astrocytoma is frequently hampered by radioresistance of the tumor. In addition to overexpression of ErbB1/EGFR, functional crosstalk between receptor tyrosine kinases and cell adhesion molecules may also contribute to therapy resistance. Methods Acceptor photobleaching FRET was implemented on frozen sections of clinical astrocytoma to check the role of ErbB1-integrin-beta1 interaction. U251 glioma subclones were obtained by introducing extra CHR7 material or the ErbB1 gene to test the relevance and mechanism of this interaction in vitro. Results Grade IV tumors showed higher ErbB1 and integrin-beta1 expression and greater ErbB1-integrin-beta1 heteroassociation than did grade II tumors. Of these, the extent of molecular association was a single determinant of tumor grade and prognosis in stepwise logistic regression. In vitro, integrin-beta1 was upregulated, and radiosensitivity was diminished by ectopic ErbB1 expression. Great excess of ErbB1 provided colony forming advantage over medium excess but did not yield better radiation resistance or faster proliferation and decreased to medium level over time, whereas integrin-beta1 levels remained elevated and defined the extent of radioresistance. Increased expression of ErbB1 and integrin-beta1 was paralleled by decreasing ErbB1 homoassociation and increasing ErbB1-integrin-beta1 heteroassociation. Microscopic two-sided FRET revealed that pixels with higher ErbB1-integrin-beta1 heteroassociation exhibited lower ErbB1 homoassociation, indicating competition for association partners among these molecules. Boosted Akt phosphorylation response to EGF accompanied this shift toward heteroassociation, and the consequentially increased radioresistance could be reverted by inhibiting PI3K. Conclusion The clinically

relevant ErbB1-integrin-beta1 heteroassociation may be used as a target of both predictive diagnostics and molecular therapy.

[768]

**TÍTULO / TITLE:** - Expression of Fes-related protein Fer correlates with aggressiveness and poor prognosis in renal cell carcinoma. Immunostaining of papillary cell renal carcinoma by anti-Fer antibodies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Jun;104(6):Junecover. doi: 10.1111/cas.12150.

●●Enlace al texto completo (gratis o de pago) [1111/cas.12150](#)

**AUTORES / AUTHORS:** - Miyata Y; Kanda S; Sakai H; Greer PA

[769]

**TÍTULO / TITLE:** - Role of p38 and JNK MAPK signaling pathways and tumor suppressor p53 on induction of apoptosis in response to Ad-eIF5A1 in A549 lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer. 2013 May 2;12:35. doi: 10.1186/1476-4598-12-35.

●●Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-35](#)

**AUTORES / AUTHORS:** - Taylor CA; Zheng Q; Liu Z; Thompson JE

**INSTITUCIÓN / INSTITUTION:** - Department of Biology, University of Waterloo, 200 University Ave, W., Waterloo, ON N2L 3G1, Canada.  
[jet@sciborg.uwaterloo.ca](mailto:jet@sciborg.uwaterloo.ca).

**RESUMEN / SUMMARY:** - BACKGROUND: The eukaryotic translation initiation factor 5A1 (eIF5A1) is a highly conserved protein involved in many cellular processes including cell division, translation, apoptosis, and inflammation. Induction of apoptosis is the only function of eIF5A1 that is known to be independent of post-translational hypusine modification. In the present study, we investigated the involvement of mitogen- and stress-activated protein kinases during apoptosis of A549 lung cancer cells infected with adenovirus expressing eIF5A1 or a mutant of eIF5A1 that cannot be hypusinated (eIF5A1K50A). METHODS: Using adenoviral-mediated transfection of human A549 lung cancer cells to over-express eIF5A1 and eIF5A1K50A, the mechanism by which unhypusinated eIF5A1 induces apoptosis was investigated by Western blotting, flow cytometry, and use of MAPK and p53 inhibitors. RESULTS: Phosphorylation of ERK, p38 MAPK, and JNK was observed in response to adenovirus-mediated over-expression of eIF5A1 or eIF5A1K50A, along with phosphorylation and stabilization of the p53 tumor suppressor protein. Synthetic inhibitors of p38 and JNK kinase activity, but not inhibitors of ERK1/2 or p53 activity, significantly inhibited apoptosis induced by

Ad-eIF5A1. Importantly, normal lung cells were more resistant to apoptosis induced by eIF5A1 and eIF5A1K50A than A549 lung cancer cells.  
CONCLUSIONS: Collectively these data indicate that p38 and JNK MAP kinase signaling are important for eIF5A1-induced cell death and that induction of apoptosis was not dependent on p53 activity.

[770]

**TÍTULO / TITLE:** - Hrk Mediates 2-Methoxyestradiol-Induced Mitochondrial Apoptotic Signaling in Prostate Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 31.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1187](#)

**AUTORES / AUTHORS:** - Chang I; Majid S; Saini S; Zaman MS; Yamamura S; Chiyomaru T; Shahryari V; Fukuhara S; Deng G; Dahiya R; Tanaka Y

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliation: Department of Urology, San Francisco Veterans Affairs Medical Center and University of California at San Francisco, San Francisco, California.

**RESUMEN / SUMMARY:** - Prostate cancer is one of the most prevalent cancers in males and ranks as the second most common cause of cancer-related deaths. 2-methoxyestradiol (2-ME), an endogenous estrogen metabolite, is a promising anticancer agent for various types of cancers. Although 2-ME has been shown to activate c-Jun-NH2-kinase (JNK) and mitochondrial-dependent apoptotic signaling pathways, the underlying mechanisms, including downstream effectors, remain unclear. Here, we report that the human Bcl-2 homology 3 (BH3)-only protein harakiri (Hrk) is a critical effector of 2-ME-induced JNK/mitochondria-dependent apoptosis in prostate cancer cells. Hrk mRNA and protein are preferentially upregulated by 2-ME, and Hrk induction is dependent on the JNK activation of c-Jun. Hrk knockdown prevents 2-ME-mediated apoptosis by attenuating the decrease in mitochondrial membrane potential, subsequent cytochrome c (cyt c) release, and caspase activation. Involvement of the proapoptotic protein Bak in this process suggested the possible interaction between Hrk and Bak. Thus, Hrk activation by 2-ME or its overexpression displaced Bak from the complex with antiapoptotic protein Bcl-xL, whereas deletion of the Hrk BH3 domain abolished its interaction with Bcl-xL, reducing the proapoptotic function of Hrk. Finally, Hrk is also involved in the 2-ME-mediated reduction of X-linked inhibitor of apoptosis through Bak activation in prostate cancer cells. Together, our findings suggest that induction of the BH3-only protein Hrk is a critical step in 2-ME activation of the JNK-induced apoptotic pathway, targeting mitochondria by liberating proapoptotic protein Bak. Mol Cancer Ther; 12(6); 1-11. ©2013 AACR.

[771]

**TÍTULO / TITLE:** - Identification and characterization of a small molecule inhibitor of Wnt signaling in glioblastoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1176-T](#)

**AUTORES / AUTHORS:** - De Robertis A; Valensin S; Rossi M; Tunici P; Verani M; De Rosa A; Giordano C; Varrone M; Nencini A; Pratelli C; Benicchi T; Bakker A; Hill J; Sangthongpitag K; Pendharkar V; Boping L; Fui Mee N; Siew Wen T; Shi Jing T; Cheong SM; He X; Caricasole A; Salerno M

**INSTITUCIÓN / INSTITUTION:** - 1Pharmacology, Siena Biotech.

**RESUMEN / SUMMARY:** - Glioblastoma multiforme (GBM) is the most common and prognostically unfavorable form of brain tumor. The aggressive and highly invasive phenotype of these tumors makes them among the most anatomically damaging human cancers with a median survival of less than one year. Although canonical WNT pathway activation in cancers has been historically linked to the presence of mutations involving key components of the pathway (APC, beta-CATENIN or AXIN proteins), an increasing number of studies suggest that elevated WNT signaling in GBM is initiated by several alternative mechanisms that are involved in different steps of the disease. Therefore, inhibition of WNT signaling may represent a therapeutically relevant approach for GBM treatment. After the selection of a GBM cell model responsive to WNT inhibition, we set out to develop a screening approach for the identification of compounds capable of modulating canonical WNT signaling and associated proliferative responses in GBM cells. Here we show that the small molecule SEN461 inhibits the canonical WNT signaling pathway in GBM cells, with relevant effects at both molecular and phenotypic levels in vitro and in vivo. These include SEN461-induced AXIN stabilization, increased beta-CATENIN phosphorylation/degradation, and inhibition of anchorage-independent growth of human GBM cell lines and patient-derived primary tumor cells in vitro. Moreover, in vivo administration of SEN461 antagonized WNT signaling in Xenopus embryos and reduced tumor growth in a GBM xenograft model. These data represent the first demonstration that small molecule-mediated inhibition of WNT signaling may be a potential approach for GBM therapeutics.

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[772]

**TÍTULO / TITLE:** - Detection of BCR-ABL1 Kinase Domain Mutations Causing Imatinib Resistance in Chronic Myelogenous Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2013;999:25-39. doi: 10.1007/978-1-62703-357-2\_2.

●●Enlace al texto completo (gratis o de pago) [1007/978-1-62703-357-](http://1007/978-1-62703-357-2_2)

[2\\_2](#)

**AUTORES / AUTHORS:** - Moore FR; Yang F; Press RD

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Baystate Medical Center/Tufts University School of Medicine, Springfield, MA, USA.

**RESUMEN / SUMMARY:** - The reciprocal translocation between chromosomes 9 and 22 [t(9;22)(q34;q11), Philadelphia chromosome] creates a BCR-ABL1 fusion protein that occurs in approximately 95% of cases of chronic myelogenous leukemia (CML), 15% of cases of adult acute lymphoblastic leukemia, and 5% of adult cases of acute myeloid leukemia. The BCR-ABL1 protein is a constitutively activated tyrosine kinase that induces and maintains the neoplastic phenotype in these leukemias. PCR-based methods to identify and quantitate the tumor-specific BCR-ABL1 RNA have been shown to be an ultrasensitive diagnostic, prognostic, and monitoring tool for Philadelphia-positive leukemias. A novel tyrosine kinase inhibitor (TKI), imatinib, has been confirmed as an effective targeted treatment in most CML patients. However, a significant minority of patients being treated with imatinib develop resistance to the drug as evidenced by rising BCR-ABL1 levels. The most common mechanism of resistance in these patients is the development of mutations in the BCR-ABL1 kinase domain (KD) that abrogate binding of imatinib. Although KD mutations are quite heterogeneous, the identification of the exact mutation site is clinically important, as some mutations, but not others, can be effectively treated with second-generation TKIs. One mutation, T315I, for example, renders the leukemia resistant to all first- and second-line TKIs. Thus, DNA sequencing of the BCR-ABL1 kinase domain in resistant patients helps identify those who may benefit from a change in TKI agents, or those who should be considered for other therapeutic measures, such as stem cell transplantation. We describe here a method for sequencing the BCR-ABL1 kinase domain in peripheral blood or bone marrow of CML patients.

[773]

**TÍTULO / TITLE:** - Human three prime exonuclease TREX1 is induced by genotoxic stress and involved in protection of glioma and melanoma cells to anticancer drugs.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 Aug;1833(8):1832-43. doi: 10.1016/j.bbamcr.2013.03.029. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago)

[1016/j.bbamcr.2013.03.029](http://1016/j.bbamcr.2013.03.029)

**AUTORES / AUTHORS:** - Tomicic MT; Aasland D; Nikolova T; Kaina B; Christmann M

**INSTITUCIÓN / INSTITUTION:** - Department of Toxicology, University Medical Center, Obere Zahlbacher Str. 67, D-55131 Mainz, Germany.

**RESUMEN / SUMMARY:** - To counteract genotoxic stress, DNA repair functions are in effect. Most of them are constitutively expressed while some of them can be up-regulated depending on the level of DNA damage. In human cells, only few DNA repair functions are subject of induction following DNA damage, and thus there is a need to identify and characterize inducible repair functions more thoroughly. Here, we provide evidence that the “three prime exonuclease I” (TREX1) is up-regulated in human fibroblasts and cancer cells on mRNA and protein level. Transcriptional upregulation of TREX1 was observed upon exposure to ultraviolet light and various anticancer drugs in glioma and malignant melanoma cells. Induction of TREX1 was found following treatment with the crosslinking alkylating agents nimustine, carmustine, fotemustine and the topoisomerase I inhibitor topotecan, but not following temozolomide, etoposide and ionizing radiation. Induction of TREX1 following DNA damage requires the AP-1 components c-Jun and c-Fos, as shown by siRNA knockdown, EMSA experiments, ChIP analysis and reporter assays with the TREX1 promoter and constructs harboring mutations in the AP-1 binding site. To analyze whether TREX1 expression impacts the sensitivity of cancer cells to therapeutics, TREX1 expression was down-regulated by siRNA in malignant glioma and melanoma cells. TREX1 knockdown resulted in enhanced cell death following nimustine, fotemustine and topotecan and to a reduced recovery from the anticancer drug induced block to replication. The data revealed that induction of TREX1 is a survival response evoked by various genotoxic anticancer drugs and identified TREX1 as a potential therapeutic target for anticancer therapy.

[774]

**TÍTULO / TITLE:** - Prognostic potential of ERG (ETS-related gene) expression in prostatic adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int Urol Nephrol. 2013 May 18.

●●Enlace al texto completo (gratis o de pago) [1007/s11255-013-0406-](#)

[2](#)

**AUTORES / AUTHORS:** - Szasz AM; Majoros A; Rosen P; Srivastava S; Dobi A; Szendroi A; Kulka J; Nyirady P

**INSTITUCIÓN / INSTITUTION:** - 2<sup>nd</sup> Department of Pathology, Semmelweis University, 93 Ulloi ut, 1091, Budapest, Hungary, [cac@korb2.sote.hu](mailto:cac@korb2.sote.hu).

**RESUMEN / SUMMARY:** - **PURPOSE:** Following patients after prostatectomy can be expensive and stressful, therefore, a novel and reliable approach to improve stratification is needed both at diagnosis of PCa and following its treatment. We evaluate the association of both ERG and claudin-4, claudin-5, and beta-catenin expression in tumor tissues of patients with organ-confined and advanced prostatic adenocarcinomas. **METHODS:** A total of 30 patients were included in the study. Nine men who underwent radical prostatectomy for organ-confined

(pT2N0M0) cancer (OCC), 10 patients with clinically advanced cancer (CAC), and 11 controls with benign prostatic hypertrophy (BPH). Using immunohistochemistry applied to tissue microarrays, each group was evaluated for beta-catenin, claudin-4, claudin-5, and ERG expression. RESULTS: The expression of ERG was higher in the CAC group when compared to OCC and BPH ( $p = 0.7684$ ,  $p = 0.0224$ , respectively). Among these patients, 5 from the CAC (45 %) and 5 from the OCC group (56 %) stained positively for ERG ( $p = 1.0$ ). The mean staining score for those with ERG+ advanced cancer was greater than that for the ERG+ organ-confined cancer ( $p = 0.0209$ ). ERG staining correlated with Gleason score (Pearson's correlation: 0.498,  $p = 0.0051$ ), but not with serum PSA level (Pearson's correlation: 0.404,  $p = 0.1202$ ). When analyzing outcome data, high ERG expressing tumors have shown a significantly worse overall survival ( $p = 0.0084$ ). CONCLUSIONS: Our results of presence or absence of claudin-4 and claudin-5 and ERG staining intensities suggest their potential as prognostic factors for prostate cancer.

[775]

**TÍTULO / TITLE:** - Curcumin inhibits AP-2gamma-induced apoptosis in the human malignant testicular germ cells in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Pharmacol Sin. 2013 May 20. doi: 10.1038/aps.2013.38.

●●Enlace al texto completo (gratis o de pago) [1038/aps.2013.38](#)

**AUTORES / AUTHORS:** - Zhou C; Zhao XM; Li XF; Wang C; Zhang XT; Liu XZ; Ding XF; Xiang SL; Zhang J

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Key Laboratory of Protein Chemistry and Developmental Biology, Ministry of Education of China, College of Life Science, Hunan Normal University, Changsha 410081, China.

**RESUMEN / SUMMARY:** - Aim: To investigate the effects of curcumin on proliferation and apoptosis in testicular cancer cells in vitro and to investigate its molecular mechanisms of action. Methods: NTERA-2 human malignant testicular germ cell line and F9 mouse teratocarcinoma stem cell line were used. The anti-proliferative effect was examined using MTT and colony formation assays. Hoechst 33258 staining, TUNEL and Annexin V-FITC/PI staining assays were used to analyze cell apoptosis. Protein expression was examined with Western blot analysis and immunocytochemical staining. Results: Curcumin (5, 10 and 15  $\mu\text{mol/L}$ ) inhibited the viability of NTERA-2 cells in dose- and time-dependent manners. Curcumin significantly inhibited the colony formation in both NTERA-2 and F9 cells. Curcumin dose-dependently induced apoptosis of NTERA-2 cells by reducing FasL expression and Bcl-2-to-Bax ratio, and activating caspase-9, -8 and -3. Furthermore, curcumin dose-dependently reduced the expression of AP transcription factor AP-2gamma in NTERA-2 cells, whereas the pretreatment

with the proteasome inhibitor MG132 blocked both the curcumin-induced reduction of AP-2gamma and antiproliferative effect. Curcumin inhibited ErbB2 expression, and decreased the phosphorylation of Akt and ERK in NTera-2 cells. Conclusion: Curcumin induces apoptosis and inhibits proliferation in NTera-2 cells via the inhibition of AP-2gamma-mediated downstream cell survival signaling pathways.

[776]

**TÍTULO / TITLE:** - Alterations of the genes involved in the PI3K and estrogen-receptor pathways influence outcome in human epidermal growth factor receptor 2-positive and hormone receptor-positive breast cancer patients treated with trastuzumab-containing neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 16;13:241. doi: 10.1186/1471-2407-13-241.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-241](#)

**AUTORES / AUTHORS:** - Takada M; Higuchi T; Tozuka K; Takei H; Haruta M; Watanabe J; Kasai F; Inoue K; Kurosumi M; Miyazaki M; Sato-Otsubo A; Ogawa S; Kaneko Y

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer Diagnosis, Research Institute for Clinical Oncology, Saitama Cancer Center, 818 Komuro, Ina, Saitama, 362-0806, Japan. [kaneko@cancer-c.pref.saitama.jp](mailto:kaneko@cancer-c.pref.saitama.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: Chemotherapy with trastuzumab is widely used for patients with human epidermal growth factor receptor 2-positive (HER2+) breast cancer, but a significant number of patients with the tumor fail to respond, or relapse. The mechanisms of recurrence and biomarkers that indicate the response to the chemotherapy and outcome are not fully investigated. METHODS: Genomic alterations were analyzed using single-nucleotide polymorphism arrays in 46 HER2 immunohistochemistry (IHC) 3+ or 2+/fluorescent in situ hybridization (FISH)+ breast cancers that were treated with neoadjuvant chemotherapy with paclitaxel, cyclophosphamid, epirubicin, fluorouracil, and trastuzumab. Patients were classified into two groups based on presence or absence of alterations of 65 cancer-associated genes, and the two groups were further classified into four groups based on genomic HER2 copy numbers or hormone receptor status (HR+/-). Pathological complete response (pCR) and relapse-free survival (RFS) rates were compared between any two of the groups. RESULTS AND DISCUSSION: The pCR rate was 54% in 37 patients, and the RFS rate at 3 years was 72% (95% CI, 0.55-0.89) in 42 patients. The analysis disclosed 8 tumors with nonamplified HER2 and 38 tumors with HER2 amplification, indicating the presence of discordance in tumors diagnosed using current HER2 testing. The 8 patients showed more difficulty in achieving pCR (P=0.019), more frequent relapse (P=0.018), and more frequent alterations of genes in the PI3K pathway (P=0.009) than the

patients with HER2 amplification. The alterations of the PI3K and estrogen receptor (ER) pathway genes generally indicated worse RFS rates. The prognostic significance of the alterations was shown in patients with a HR+ tumor, but not in patients with a HR- tumor when divided. Alterations of the PI3K and ER pathway genes found in patients with a HR+ tumor with poor outcome suggested that crosstalk between the two pathways may be involved in resistance to the current chemotherapy with trastuzumab. CONCLUSIONS: We recommend FISH analysis as a primary HER2 testing because patients with IHC 2+/3+ and nonamplified HER2 had poor outcome. We also support concurrent use of trastuzumab, lapatinib, and cytotoxic and anti-hormonal agents for patients having HR+ tumors with alterations of the PI3K and ER pathway genes.

[777]

**TÍTULO / TITLE:** - CYP2D6 genotype predicts tamoxifen side effects but not cancer-free or survival benefits in postmenopausal ER+ and/or PgR+ breast cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Apr;14(5):462-3.

**AUTORES / AUTHORS:** - Catalano J; Hawkins TB; Wang J; Jawaid A; Fox JC; Hong H

**INSTITUCIÓN / INSTITUTION:** - Division of Cellular & Gene Therapies, Center for Biologics Evaluation & Research, US FDA, 9000 Rockville Pike, Bethesda, MD 20892, USA.

[778]

**TÍTULO / TITLE:** - Apoptosis of human gastric cancer cells line SGC 7901 induced by garlic-derived compound S-allylmercaptocysteine (SAMC).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur Rev Med Pharmacol Sci. 2013 Mar;17(6):745-51.

**AUTORES / AUTHORS:** - Yan JY; Tian FM; Hu WN; Zhang JH; Cai HF; Li N

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology, Tangshan People's Hospital, Tangshan, China. [yanjinyin2013@yeah.net](mailto:yanjinyin2013@yeah.net)

**RESUMEN / SUMMARY:** - BACKGROUND: Epidemiological and experimental carcinogenesis studies provide evidence that components of garlic (*Allium sativum*) have anticancer activity. Hepatocellular carcinoma is highly malignant and metastatic. Currently, there is no effective chemotherapy for patients with advanced Hepatocellular carcinoma leading to an urgent need to seek for novel therapeutic options. AIM: To investigate the effect of cell growth, cell apoptosis of Garlic-Derived Compound S-Allylmercaptocysteine (SAMC) on Human Gastric Cancer Cells Line SGC 7901 cells. MATERIALS AND METHODS: The SGC 7901 cells were cultured with different concentration's SAMC. Cell viability was detected by AO/EB staining. JNK and P38 pathway were assayed by PCR

(polymerase chain reaction). RESULTS: The best concentration of SAMC (300 microM) for induction SGC 7901 apoptosis was confirmed through cell viability. The PCR assay demonstrated that JNK and P38 pathway play important role in apoptosis of SGC 7901 cells. CONCLUSIONS: This study indicated that SAMC can inhibit cell proliferation and induct apoptosis of SGC 7901 cells via JNK and P38 pathway.

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[779]

**TÍTULO / TITLE:** - Telomelysin exhibits potent anti-tumor activity via apoptotic and non-apoptotic cell death in soft tissue sarcoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Sci. 2013 May 29. doi: 10.1111/cas.12208.

●●Enlace al texto completo (gratis o de pago) [1111/cas.12208](#)

**AUTORES / AUTHORS:** - Li GD; Kawashima H; Ogose A; Ariizumi T; Hotta T; Kuwano R; Urata Y; Fujiwara T; Endo N

**INSTITUCIÓN / INSTITUTION:** - Division of Orthopedic Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata, 951-8510, Japan; Department of Orthopedic Surgery, The Second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, Nangang District, Harbin, Heilongjiang, 150086, China.

**RESUMEN / SUMMARY:** - This study investigated the pathway underlying the anti-tumor activity of telomelysin, a telomerase-dependent, replication-selective oncolytic adenovirus, in soft tissue sarcoma cells. Treatment with telomelysin alone resulted in simultaneous induction of apoptosis and autophagy while co-treatment with telomelysin and 3-MA significantly reduced cell viability and increased apoptosis and cellular ATP level compared to telomelysin-alone treatment, indicating that telomelysin-mediated autophagy is a death-protective but not death-promoting process. Co-treatment with Z-VAD-FMK significantly increased cellular ATP depletion compared to telomelysin-alone treatment while inhibiting telomelysin-induced apoptosis and having no significant effect on cell viability, indicating that it promotes transition from apoptotic to necrotic cell death. This article is protected by copyright. All rights reserved.

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[780]

**TÍTULO / TITLE:** - Hydroxytyrosol Promotes Superoxide Production and Defects in Autophagy Leading to Anti-Proliferative and Apoptotic Effects on Human Prostate Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Cancer Drug Targets. 2013 Apr 17.

**AUTORES / AUTHORS:** - Luo C; Li Y; Wang H; Cui Y; Feng Z; Li H; Li Y; Wang Y; Wurtz K; Weber P; Long J; Liu J

**INSTITUCIÓN / INSTITUTION:** - Center for Mitochondrial Biology and Medicine  
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**RESUMEN / SUMMARY:** - Hydroxytyrosol, an important polyphenolic compound found in olive oil, has shown anti-tumor activity both in vitro and in vivo. However, effects of hydroxytyrosol on prostate cancer are largely unknown. We found that hydroxytyrosol preferentially reduces the viability of human prostate cancer cells (PC-3, DU145) compared to an immortalized non-malignant prostate epithelial cell line (RWPE-1). Exposure of PC-3 cells to 80 micromol/L hydroxytyrosol resulted in significant increases in both superoxide production and activation of apoptosis. These increases were accompanied by mitochondrial dysfunction, defects in autophagy, and activation of MAP kinases. Moreover, N-acetyl-cysteine (NAC), an efficient reactive oxygen species (ROS) scavenger, was able to reverse the hydroxytyrosol-induced effects of cell viability loss, defects in autophagy, and activation of apoptosis. This evidence suggests that ROS play a vital role in the loss of PC-3 cell viability. However, MAPK inhibitors including U0126 (for Erk1/2), SB203580 (for p38MAPK) and SP600125 (for JNK) did not decrease hydroxytyrosol-induced growth inhibition, suggesting that these kinases may not be required for the growth inhibitory effect of hydroxytyrosol. Moreover, addition of ROS scavengers (i.e. NAC, catalase, pyruvate, SOD) in the growth media can prevent hydroxytyrosol induced cell viability loss, suggesting that extracellular ROS (superoxide and hydrogen peroxide) facilitate the anti-proliferation effect of hydroxytyrosol in prostate cancer cells. The present work firstly shows that hydroxytyrosol induces apoptotic cell death and mitochondrial dysfunction by generating superoxide in PC-3 cells. This research presents preliminary evidence on the in vitro chemopreventive effect of hydroxytyrosol, and will contribute to further investigation of hydroxytyrosol as an anti-cancer agent.

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[781]

**TÍTULO / TITLE:** - Jaridonin, a Novel Diterpenoid from *Isodon rubescens*, Induces Reactive Oxygen Species-Mediated Apoptosis in Esophageal Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Cancer Drug Targets. 2013 Apr 17.

**AUTORES / AUTHORS:** - Ma YC; Ke Y; Zi X; Zhao W; Shi XJ; Liu HM

**INSTITUCIÓN / INSTITUTION:** - School of Pharmaceutical Sciences, Zhengzhou University, 100 Kexue Avenue, Zhengzhou, Henan 450001, P. R. China.  
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**RESUMEN / SUMMARY:** - *Isodon rubescens*, a Chinese herb, has been used as a folk, botanical medicine by the local people in Henan Province, China for the treatment of respiratory and gastrointestinal bacterial infections, inflammation, and cancer for many years. Recently, we isolated a new ent-kaurene diterpenoid, named Jaridonin, from *Isodon rubescens*. The chemical structure of

Jaridonin was verified by Infrared (IR), Nuclear magnetic resonance (NMR), and Mass spectrum (MS) data as well as X-ray spectra. Jaridonin exhibited a strong inhibitory effect on the growth of several esophageal cancer cell lines, including EC109, EC9706 and EC1, in both a dose-and time-dependent fashion. Jaridonin induced typical apoptotic morphological characteristics, increased the number of annexin V-positive staining cells, as well as caused a G2/M arrest in cell cycle progression. Furthermore, Jaridonin resulted in a significant loss of mitochondrial membrane potential, release of cytochrome c into the cytosol, and then activation of Caspase-9 and Caspase-3. These results indicate that Jaridonin isolation activates the mitochondria mediated apoptosis. Furthermore, these effects of Jaridonin were accompanied by marked accumulation of reactive oxygen species (ROS) and increased expression of p53, p21waf1/Cip1 and Bax, whereas two ROS scavengers, N-acetyl-L-cysteine (L-NAC) and Vitamin C, significantly attenuated the effects of Jaridonin on the mitochondrial membrane potential, DNA damage, expression of p53 and p21waf1/Cip1 and reduction of cell viabilities. Taken together, our results suggest that a natural ent-kaurenoid diterpenoid, Jaridonin, is a novel apoptosis inducer and deserves further investigation as a new chemotherapeutic strategy for patients with esophageal cancer.

[782]

**TÍTULO / TITLE:** - Homeostatic housecleaning effect of selenium: Evidence that noncytotoxic oxidant-induced damage sensitizes prostate cancer cells to organic selenium-triggered apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biofactors. 2013 Apr 29. doi: 10.1002/biof.1106.

●●Enlace al texto completo (gratis o de pago) [1002/biof.1106](#)

**AUTORES / AUTHORS:** - Chiang EC; Bostwick DG; Waters DJ

**INSTITUCIÓN / INSTITUTION:** - Department of Nutrition Science, Purdue University, West Lafayette, IN; Center on Aging and the Life Course, Purdue University, West Lafayette, IN; Gerald P. Murphy Cancer Foundation, West Lafayette, IN.

**RESUMEN / SUMMARY:** - The anti-cancer activity of organic selenium has been most consistently documented at supra-nutritional levels at which selenium-dependent, antioxidant enzymes are maximized in both expression and activity. Thus, there is a strong imperative to identify mechanisms other than antioxidant protection to account for selenium's anti-cancer activity. In vivo work in dogs showed that dietary selenium supplementation decreased DNA damage but increased apoptosis in the prostate, leading to a new hypothesis: Organic selenium exerts its cancer preventive effect by selectively increasing apoptosis in DNA-damaged cells. Here, we test whether organic selenium (methylseleninic acid; MSA) triggers more apoptosis in human and canine prostate cancer cells that have more DNA damage (strand breaks) created by

hydrogen-peroxide (H<sub>2</sub>O<sub>2</sub>) at noncytotoxic doses prior to MSA exposure. Apoptosis triggered by MSA was significantly higher in H<sub>2</sub>O<sub>2</sub>-damaged cells. A supra-additive effect was observed-the extent of MSA-triggered apoptosis in H<sub>2</sub>O<sub>2</sub>-damaged cells exceeded the sum of apoptosis induced by MSA or H<sub>2</sub>O<sub>2</sub> alone. However, neither the persistence of H<sub>2</sub>O<sub>2</sub>-induced DNA damage, nor the activation of mitogen-activated protein kinases was required to sensitize cells to MSA-triggered apoptosis. Our results document that selenium can exert a “homeostatic housecleaning” effect- a preferential elimination of DNA-damaged cells. This work introduces a new and potentially important perspective on the anti-cancer action of selenium in the aging prostate that is independent of its role in antioxidant protection. © 2013 BioFactors, 2013.

[783]

**TÍTULO / TITLE:** - Activation of Autophagy by Globular Adiponectin Attenuates Ethanol-induced Apoptosis in HepG2 Cells: Involvement of AMPK/FoxO3A Axis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 May 17. pii: S0167-4889(13)00197-3. doi: 10.1016/j.bbamcr.2013.05.013.

●●Enlace al texto completo (gratis o de pago)

[1016/j.bbamcr.2013.05.013](http://1016/j.bbamcr.2013.05.013)

**AUTORES / AUTHORS:** - Nepal S; Park PH

**INSTITUCIÓN / INSTITUTION:** - College of Pharmacy, Yeungnam University, Gyeongsanbuk-do 712-749, Republic of Korea.

**RESUMEN / SUMMARY:** - Hepatocellular apoptosis is an important pathological entity of alcoholic liver disease. Previously, we have shown that globular adiponectin (gAcrp) protects liver cells from ethanol-induced apoptosis by modulating an array of signaling pathways. In the present study, we investigated the role of autophagy induction by gAcrp in the suppression of ethanol-induced apoptosis and its potential mechanism(s) in liver cells. Here, we demonstrated that gAcrp significantly restores ethanol-induced suppression of autophagy-related genes, including Beclin-1 and microtubule-associated protein light chain (LC3B) both in primary rat hepatocytes and human hepatoma cell line (HepG2). Globular adiponectin also restored autophagosome formation suppressed by ethanol treatment in HepG2. Furthermore, inhibition of gAcrp-induced autophagic process by knock-down of LC3B prevented protection from ethanol-induced apoptosis. In particular, the autophagic process induced by gAcrp was involved in the suppression of ethanol-induced activation of caspase-8 and expression of Bax. Moreover, knock-down of AMPK by small interfering RNA (siRNA) blocked gAcrp-induced expression of genes related to autophagy, which in turn prevented protection from ethanol-induced apoptosis, suggesting that AMPK plays an important role in the induction of autophagy and protection of liver cells by gAcrp. Finally, we

also showed that gAcrp treatment induces translocation of the forkhead box O member protein, FoxO3A, into the nucleus, which may play a role in the induction of autophagy-related genes. Taken together, our data demonstrated that gAcrp protects liver cells from ethanol-induced apoptosis via induction of autophagy. Further, the AMPK-FoxO3A axis plays a cardinal role in gAcrp-induced autophagy and subsequent inhibition of ethanol-induced apoptosis.

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[784]

**TÍTULO / TITLE:** - Naringenin (Citrus Flavonone) Induces Growth Inhibition, Cell Cycle Arrest and Apoptosis in Human Hepatocellular Carcinoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 May 10.

●●Enlace al texto completo (gratis o de pago) [1007/s12253-013-9641-](#)

[1](#)

**AUTORES / AUTHORS:** - Arul D; Subramanian P

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Annamalaiagar, 608 002, Tamil Nadu, India, [sent.biochem@gmail.com](mailto:sent.biochem@gmail.com).

**RESUMEN / SUMMARY:** - Search for new substances with antiproliferative activity and apoptosis inducing potential towards HepG2 cells is important since HCC is notoriously resistant to conventional chemotherapy. Dietary phytochemicals with significant anti-proliferative and apoptosis inducing potential are considered as agents promising for cancer therapy. Naringenin, a common dietary flavonoid abundantly present in fruits and vegetables, is believed to possess strong cytotoxic activity in numerous types of cancer cells. However, the detailed molecular mechanisms of its antiproliferative effects and apoptosis induction are still unclear. In this study, we investigated antiproliferative and apoptosis-inducing effect of naringenin in human hepatocellular carcinoma HepG2 cells. Naringenin was shown to inhibit the proliferation of HepG2 cells resulted partly from an accumulation of cells in the G0/G1 and G2/M phase of the cell cycle. Naringenin induced a rapid accumulation of p53, which might account for the naringenin-induced G0/G1 and G2/M phase arrests in Hep G2 cells. In addition, naringenin have been shown to induce apoptosis as evidenced by nuclei damage and increased proportion of apoptotic cells detected by flow cytometry analysis. Naringenin triggered the mitochondrial-mediated apoptosis pathway as shown by an increased ratio of Bax/Bcl-2, subsequent release of cytochrome C, and sequential activation of caspase-3. Our results showed that naringenin had inhibitory effect on the growth of HepG2 cell line through inhibition of cell proliferation and apoptosis induction. The elucidation of the drug targets of naringenin on inhibition of tumor cells growth should enable further development of naringenin for liver cancer therapy.

[785]

**TÍTULO / TITLE:** - Randomized controlled trial of toremifene 120 mg compared with exemestane 25 mg after prior treatment with a non-steroidal aromatase inhibitor in postmenopausal women with hormone receptor-positive metastatic breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 16;13(1):239.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-239](https://doi.org/10.1186/1471-2407-13-239)

**AUTORES / AUTHORS:** - Yamamoto Y; Ishikawa T; Hozumi Y; Ikeda M; Iwata H; Yamashita H; Toyama T; Chishima T; Saji S; Yamamoto-Ibusuki M; Iwase H

**RESUMEN / SUMMARY:** - BACKGROUND: After the failure of a non-steroidal aromatase inhibitor (nsAI) for postmenopausal patients with metastatic breast cancer (mBC), it is unclear which of various kinds of endocrine therapy is the most appropriate. A randomized controlled trial was performed to compare the efficacy and safety of daily toremifene 120 mg (TOR120), a selective estrogen receptor modulator, and exemestane 25 mg (EXE), a steroidal aromatase inhibitor. The primary end point was the clinical benefit rate (CBR). The secondary end points were objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and toxicity. METHODS: Initially, a total of 91 women was registered in the study and randomly assigned to either TOR120 (n = 46) or EXE (n = 45) from October 2008 to November 2011. Three of the 46 patients in the TOR120 arm were not received treatment, 2 patients having withdrawn from the trial by their preference and one having been dropped due to administration of another SERM. RESULTS: When analyzed after a median observation period of 16.9 months, the intention-to-treat analysis showed that there were no statistical difference between TOR120 (N = 46) and EXE (n = 45) in terms of CBR (41.3% vs. 26.7%; P = 0.14), ORR (10.8% vs. 2.2%; P = 0.083), and OS (Hazard ratio, 0.60; P = 0.22). The PFS of TOR120 was longer than that of EXE, the difference being statistically significant (Hazard ratio, 0.61, P = 0.045). The results in treatment-received cohort (N = 88) were similar to those in ITT cohort. Both treatments were well-tolerated with no severe adverse events, although the treatment of 3 of 43 women administered TOR120 was stopped after a few days because of nausea, general fatigue, hot flush and night sweating. CONCLUSIONS: TOR120, as a subsequent endocrine therapy for mBC patients who failed non-steroidal AI treatment, could potentially be more beneficial than EXE. Trial registration number: UMIN000001841 URL: <https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000001797&language=J>.

[786]

**TÍTULO / TITLE:** - Proteomic approach toward molecular backgrounds of drug resistance of osteosarcoma cells in spheroid culture system.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proteomics. 2013 May 28. doi: 10.1002/pmic.201300053.

●●Enlace al texto completo (gratis o de pago) [1002/pmic.201300053](http://1002/pmic.201300053)

**AUTORES / AUTHORS:** - Arai K; Sakamoto R; Kubota D; Kondo T

**INSTITUCIÓN / INSTITUTION:** - Division of Pharmacoproteomics, National Cancer Center Research Institute, Tokyo, Japan; SCIVAX Corporation, Kanagawa, Japan.

**RESUMEN / SUMMARY:** - Chemoresistance is one of the most critical prognostic factors in osteosarcoma, and elucidation of the molecular backgrounds of chemoresistance may lead to better clinical outcomes. Spheroid cells resemble in vivo cells and are considered an in vitro model for the drug discovery. We found that spheroid cells displayed more chemoresistance than conventional monolayer cells across 11 osteosarcoma cell lines. To investigate the molecular mechanisms underlying the resistance to chemotherapy, we examined the proteomic differences between the monolayer and spheroid cells by 2D-DIGE. Of the 4762 protein species observed, we further investigated 435 species with annotated mass spectra in the public proteome database, Genome Medicine Database of Japan Proteomics. Among the 435 protein species, we found that 17 species exhibited expression level differences when the cells formed spheroids in more than 5 cell lines and 4 species out of these 17 were associated with spheroid-formation associated resistance to doxorubicin. We confirmed the up-regulation of cathepsin D in spheroid cells by western blotting. Cathepsin D has been implicated in chemoresistance of various malignancies but has not previously been implemented in osteosarcoma. Our study suggested that the spheroid system may be a useful tool to reveal the molecular backgrounds of chemoresistance in osteosarcoma. This article is protected by copyright. All rights reserved.

[787]

**TÍTULO / TITLE:** - Diagnostic and Prognostic Role of Immunohistochemical Expression of Napsin-A Aspartic Peptidase in Clear Cell and Papillary Renal Cell Carcinoma: A Study Including 233 Primary and Metastatic Cases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Appl Immunohistochem Mol Morphol. 2013 May 22.

●●Enlace al texto completo (gratis o de pago)

[1097/PAI.0b013e31828ef24e](http://1097/PAI.0b013e31828ef24e)

**AUTORES / AUTHORS:** - Xu B; Abourbih S; Sircar K; Kassouf W; Aprikian A; Tanguay S; Brimo F

**INSTITUCIÓN / INSTITUTION:** - Departments of \*Pathology daggerUrology, McGill University Health Center, Montreal, QC, Canada double daggerDepartment of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX.

**RESUMEN / SUMMARY:** - Napsin-A aspartic peptidase (napsin-A) is an aspartic protease that is predominantly expressed in the proximal renal tubules and type II pneumocytes of the lung. Recently, napsin-A was reported to be present in a

proportion of renal cell carcinomas (RCCs). However, the utilization of napsin-A immunohistochemistry as a routine diagnostic tool for RCC, and the correlation of the level of napsin-A expression with histologic features have not yet been established. In the current study, using tissue microarrays composed of primary and metastatic RCCs, napsin-A expression was demonstrated in 86 of 222 (39%) clear cell RCCs (CRCCs) and 16 of 21 (76%) papillary RCCs (PRCCs), with a strong and diffuse staining pattern observed in PRCCs and a relatively weak and focal positivity in CRCCs. Compared with primary CRCCs, a comparable proportion of metastatic CRCCs retained napsin-A expression (45/132, 34%), suggesting the potential utility of napsin-A in the evaluation of metastatic tumors. The expression of napsin-A was also found to be inversely correlated to aggressive local tumor characteristics, such as advanced pathologic stage and high Fuhrman nuclear grade. We conclude that napsin-A may be a valuable immunohistochemical marker in the diagnosis of RCCs, particularly PRCC.

[788]

**TÍTULO / TITLE:** - Cyclin-dependent kinase inhibitor therapy for hematologic malignancies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Investig Drugs. 2013 Jun;22(6):723-38. doi: 10.1517/13543784.2013.789859. Epub 2013 May 6.

●●Enlace al texto completo (gratis o de pago)

[1517/13543784.2013.789859](https://doi.org/10.1517/13543784.2013.789859)

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**RESUMEN / SUMMARY:** - Introduction: Cyclin-dependent kinases (CDKs) regulate cell cycle progression. Certain CDKs (e.g., CDK7, CDK9) also control cellular transcription. Consequently, CDKs represent attractive targets for anticancer drug development, as their aberrant expression is common in diverse malignancies, and CDK inhibition can trigger apoptosis. CDK inhibition may be particularly successful in hematologic malignancies, which are more sensitive to inhibition of cell cycling and apoptosis induction. Areas covered: A number of CDK inhibitors, ranging from pan-CDK inhibitors such as flavopiridol (alvocidib) to highly selective inhibitors of specific CDKs (e.g., CDK4/6), such as PD0332991, that are currently in various phases of development, are profiled in this review. Flavopiridol induces cell cycle arrest, and globally represses transcription via CDK9 inhibition. The latter may represent its major mechanism of action via down-regulation of multiple short-lived proteins. In early phase trials, flavopiridol has shown encouraging efficacy across a wide spectrum of hematologic malignancies. Early results with dinaciclib and PD0332991 also

appear promising. Expert opinion: In general, the antitumor efficacy of CDK inhibitor monotherapy is modest, and rational combinations are being explored, including those involving other targeted agents. While selective CDK4/6 inhibition might be effective against certain malignancies, broad-spectrum CDK inhibition will likely be required for most cancers.

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[789]

**TÍTULO / TITLE:** - Targeted therapy with kinase inhibitors in aggressive endocrine tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Pharmacother. 2013 Jun;14(9):1187-203. doi: 10.1517/14656566.2013.796931.

●●Enlace al texto completo (gratis o de pago)

[1517/14656566.2013.796931](#)

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**RESUMEN / SUMMARY:** - Introduction: Kinase inhibitors (KIs) are a class of anticancer drugs that inhibit activity of the enzymes protein kinases, which regulate crucial cellular processes and have a demonstrated role in human oncogenesis. Treatment of advanced forms of endocrine cancer which are not responsive to cytotoxic chemotherapies is challenging and use of KIs is gaining a growing role in this field. Areas covered: The authors summarize the main genetic alterations known to be linked to endocrine tumors, indicating the rationale for utilizing KIs. Furthermore, they present an updated analysis of clinical trials available on PubMed Central, which were pertinent to the activities of KIs in aggressive endocrine cancer. The authors also discuss the adverse effects of KIs and summarize likely involved underlying mechanisms. Expert opinion: KIs are effective in obtaining a radiological disease control and an improvement of progression-free survival in several forms of endocrine cancer but will never deliver a knockout blow of the disease, due to mechanisms of adaptation to circumvent the specific molecular blockade. The new frontier of KIs treatment is to identify agents that could synergize activity of KIs. The true goal will be to perform an overall genotyping of each tumor, thus predicting the impact of combined targeted therapies in the context of a particular constellation of mutant genes.

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[790]

**TÍTULO / TITLE:** - Phase I/II RAF kinase inhibitors in cancer therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Investig Drugs. 2013 Jun;22(6):739-49. doi: 10.1517/13543784.2013.797964. Epub 2013 May 6.

●●Enlace al texto completo (gratis o de pago)

[1517/13543784.2013.797964](#)

**AUTORES / AUTHORS:** - Turajlic S; Ali Z; Yousaf N; Larkin J

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**RESUMEN / SUMMARY:** - Introduction: Aberrant activation of RAF signalling is a frequent finding in human cancers. BRAF is the only RAF family member that is commonly mutated, whilst CRAF and ARAF play important roles in the signal transduction from mutant RAS. BRAF-specific inhibitors have been more effective in the treatment of BRAF-mutant melanoma than BRAF-mutant thyroid and colorectal cancers. Areas covered: The review summarises the experience with RAF kinase inhibitors, including efficacy, modes of acquired resistance, and the mechanism behind the progression of pre-malignant RAS-mutant lesions observed with RAF kinase inhibitors. The authors review all the completed and ongoing Phase I or II clinical trials of RAF kinase inhibitors and discuss in detail the rationale behind the combinatorial approaches. Expert opinion: The success of RAF kinase inhibitors has demonstrated the necessity of genotype-driven treatment selection for cancer patients. The spectrum of responses in different tumour types is explained by feedback events that are determined by cell lineage. Dissection of these events and the mechanisms of acquired resistance will determine the appropriate combination therapies. Ongoing characterisation of RAS-MAPK regulation in malignant cells may aid the development of novel agents that have greater potency for the inhibition of activated RAF kinase, and lesser propensity for promotion of RAS-mutant tumours.

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[791]

**TÍTULO / TITLE:** - TNF-alpha up-regulates cellular inhibitor of apoptosis protein 2 (c-IAP2) via c-Jun N-terminal kinase (JNK) pathway in nasopharyngeal carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int Immunopharmacol. 2013 Jun;16(2):148-53. doi: 10.1016/j.intimp.2013.03.034. Epub 2013 Apr 15.

●●Enlace al texto completo (gratis o de pago)

[1016/j.intimp.2013.03.034](#)

**AUTORES / AUTHORS:** - Song Q; Wang G; Chu Y; Zhou L; Jiang M; He Q; Liu M; Qin J; Hu J

**INSTITUCIÓN / INSTITUTION:** - Cancer Center, Renmin Hospital of Wuhan University, Wuhan 430060, China.

**RESUMEN / SUMMARY:** - Inhibitor of apoptosis proteins (IAPs) contribute to both tumor progression and tumor metastasis. Here, we show that pro-inflammatory cytokine TNF-alpha induced the up-regulation of c-IAP2 in the potential metastatic nasopharyngeal carcinoma (NPC) cells in a dose- and time-dependent manner. This up-regulation is tolerant, as the pre-treatment of NPC cells with TNF-alpha reversed the up-regulation of c-IAP2 induced by TNF-alpha re-stimulation. TNF-alpha activated MAKP signals, including ERK, JNK and p38, and NF-kappaB signal, but only inhibition of JNK signal transduction reversed the induction of c-IAP2, suggesting that JNK signaling contributed to the c-IAP2 induction. The results from in vitro scratch wound-healing assays showed that TNF-alpha promoted cell invasion, which was reversed by the inhibition of JNK signaling. Taken together, these studies suggested that pro-inflammation cytokine TNF-alpha may be a promoter for NPC metastasis, and the anti-inflammatory therapy may be of benefit to the prevention of NPC metastasis.

[792]

**TÍTULO / TITLE:** - Prediction of Lung Cancer Histological Types by RT-qPCR Gene Expression in FFPE Specimens.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Mol Diagn. 2013 May 20. pii: S1525-1578(13)00068-8. doi: 10.1016/j.jmoldx.2013.03.007.

●●Enlace al texto completo (gratis o de pago)

[1016/j.jmoldx.2013.03.007](http://1016/j.jmoldx.2013.03.007)

**AUTORES / AUTHORS:** - Wilkerson MD; Schallheim JM; Hayes DN; Roberts PJ; Bastien RR; Mullins M; Yin X; Miller CR; Thorne LB; Geiersbach KB; Muldrew K; Funkhouser WK; Fan C; Hayward MC; Bayer S; Perou CM; Bernard PS

**INSTITUCIÓN / INSTITUTION:** - Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

**RESUMEN / SUMMARY:** - Lung cancer histologic diagnosis is clinically relevant because there are histology-specific treatment indications and contraindications. Histologic diagnosis can be challenging owing to tumor characteristics, and it has been shown to have less-than-ideal agreement among pathologists reviewing the same specimens. Microarray profiling studies using frozen specimens have shown that histologies exhibit different gene expression trends; however, frozen specimens are not amenable to routine clinical application. Herein, we developed a gene expression-based predictor of lung cancer histology for FFPE specimens, which are routinely available in clinical settings. Genes predictive of lung cancer histologies were derived from published cohorts that had been profiled by microarrays. Expression of these genes was measured by quantitative RT-PCR (RT-qPCR) in a cohort of patients with FFPE lung cancer. A histology expression predictor (HEP) was developed using RT-qPCR expression data for adenocarcinoma, carcinoid, small cell

carcinoma, and squamous cell carcinoma. In cross-validation, the HEP exhibited mean accuracy of 84% and kappa = 0.77. In separate independent validation sets, the HEP was compared with pathologist diagnoses on the same tumor block specimens, and the HEP yielded similar accuracy and precision as the pathologists. The HEP also exhibited good performance in specimens with low tumor cellularity. Therefore, RT-qPCR gene expression from FFPE specimens can be effectively used to predict lung cancer histology.

[793]

**TÍTULO / TITLE:** - Triptolide Induces the Expression of miR-142-3p: a Negative Regulator of Heat Shock Protein 70 and Pancreatic Cancer Cell Proliferation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 1.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1231](#)

**AUTORES / AUTHORS:** - Mackenzie TN; Mujumdar N; Banerjee S; Sangwan V; Sarver A; Vickers S; Subramanian S; Saluja AK

**INSTITUCIÓN / INSTITUTION:** - 1Surgery, University of Minnesota.

**RESUMEN / SUMMARY:** - Pancreatic ductal adenocarcinoma (PDAC), one of the deadliest malignancies, is resistant to current chemotherapies. We previously showed that triptolide inhibits PDAC cell growth in vitro and blocks metastatic spread in vivo. Triptolide downregulates heat shock protein 70 (HSP70), a molecular chaperone upregulated in several tumor types. This study investigates the mechanism by which triptolide inhibits HSP70. As microRNAs (miRNAs) are becoming increasingly recognized as negative regulators of gene expression, we tested whether triptolide regulates HSP70 via miRNAs. Here we show that triptolide, as well as quercetin but not gemcitabine, upregulated miR-142-3p in PDAC cells (MIA PaCa-2, Capan-1, and S2-013). Ectopic expression of miR-142-3p inhibited cell proliferation, measured by Electric Cell-substrate Impedance Sensing, and decreased HSP70 expression, measured by real-time PCR and immunoblotting, compared with controls. We demonstrated that miR-142-3p directly binds to the 3'UTR of HSP70, and that this interaction is important as HSP70 overexpression rescued miR-142-3p-induced cell death. We found that miR-142-3p regulates HSP70 independently of heat shock factor 1. Furthermore, Minnelide, a water soluble prodrug of triptolide, induced the expression of miR-142-3p in vivo. This is the first description of an miRNA-mediated mechanism of HSP70 regulation in cancer, making miR-142-3p an attractive target for PDAC therapeutic intervention.

[794]

**TÍTULO / TITLE:** - Collagen-hydroxyapatite/Cisplatin Drug Delivery Systems for Locoregional Treatment of Bone Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Technol Cancer Res Treat. 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago) [7785/tcrt.2012.500331](#)

**AUTORES / AUTHORS:** - Andronescu E; Fikai A; Albu MG; Mitran V; Sonmez M; Fikai D; Ion R; Cimpean A

**INSTITUCIÓN / INSTITUTION:** - Politechnica University of Bucharest, Faculty of Applied Chemistry and Material Science, 1-7 Polizu Str., 011061 Bucharest, Romania. [e\\_andronescu@rectorat.pub.ro](mailto:e_andronescu@rectorat.pub.ro).

**RESUMEN / SUMMARY:** - In this paper, the synthesis and characterization of novel cisplatin-loaded collagen (COLL)/hydroxyapatite (HA) composite materials are presented. The composite materials were designed to obtain a COLL: HA weight ratio close to the bone composition. The content of embedded cisplatin was chosen to assure a concentration of cisplatin of 6 and 10 µM, respectively, into the culture media used in cell culture experiments. These cisplatin delivery systems were characterized by determining the physico-chemical properties of the composite material, the drug release process as well as their biological activity. Based on the in vitro data that showed the cytotoxic, anti-proliferative and anti-invasive activities of these multifunctional systems on G292 osteosarcoma cells in dependence on the cisplatin concentration released in culture medium, we conclude that the newly developed COLL/HA-cisplatin drug delivery system could be a feasible approach for locoregional chemotherapy of bone cancer.

[795]

**TÍTULO / TITLE:** - Inhibition of Glucose Transporter 1 (GLUT1) Chemosensitized Head and Neck Cancer Cells to Cisplatin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Technol Cancer Res Treat. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [7785/tcrt.2012.500343](#)

**AUTORES / AUTHORS:** - Wang YD; Li SJ; Liao JX

**INSTITUCIÓN / INSTITUTION:** - Department of Oral and Maxillofacial Surgery, Stomatology Hospital, Tongji University, Shanghai, China. [lshjlchm@163.com](mailto:lshjlchm@163.com).

**RESUMEN / SUMMARY:** - Glucose transporter 1 (GLUT1) facilitates the cellular uptake of glucose and is overexpressed in most cancers. The altered expression of GLUT1 may influence the sensitivity of tumor cells to chemotherapy. This study investigated whether the knockdown of GLUT1 expression to sensitize head and neck cancer cells to the chemotherapy drug cisplatin in vitro. Anti-GLUT1 antibody was used to block activity of GLUT1 protein, and GLUT1-shRNA was used to knock down its mRNA expression in Cal27 cells. Immunocytochemistry, Western blot, and qRT-PCR were used to detect expression of GLUT1 mRNA and protein, respectively. Lentivirus was used to carrying GLUT1-shRNA to knockdown GLUT1 expression in Cal27 cells for MTT and flow cytometry analyses of cell viability and apoptosis, respectively.

Glucose uptake assay was used to assess the changes in glucose levels in Cal27 cells. It showed that GLUT1 mRNA and protein were expressed in Cal27 cells, and GLUT1 protein was localized on the cell membrane. Both anti-GLUT1 antibody and GLUT1-shRNA sensitized Cal27 cells to cisplatin treatment under both normoxia and hypoxia conditions. Anti- GLUT1 antibody and GLUT1-shRNA inhibited tumor cell growth in vitro and induced them to undergo apoptosis. GLUT1-shRNA also suppressed tumor cell uptake of glucose into the cells. Our findings suggest that inhibition of GLUT1 activity and expression can sensitize Cal27 cells to cisplatin treatment in both normoxic and hypoxic conditions. These data could be further verified in animal xenografts before potential application as a clinical adjuvant or neoadjuvant therapy of head and neck cancer with cisplatin.

[796]

**TÍTULO / TITLE:** - Treatment of basal cell carcinoma with surgical excision and perilesional interferon-alpha.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Plast Reconstr Aesthet Surg. 2013 Jul;66(7):912-6. doi: 10.1016/j.bjps.2013.03.008. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1016/j.bjps.2013.03.008](http://1016/j.bjps.2013.03.008)

**AUTORES / AUTHORS:** - Wettstein R; Erba P; Itin P; Schaefer DJ; Kalbermatten DF

**INSTITUCIÓN / INSTITUTION:** - Department of Plastic, Reconstructive, Aesthetic and Hand Surgery, University Hospital of Basel, Basel, Switzerland. Electronic address: [drwette@yahoo.com](mailto:drwette@yahoo.com).

**RESUMEN / SUMMARY:** - The classical treatment of basal cell carcinoma (BCC) is surgical removal. Recent scientific interest has shifted towards alternative, non-surgical interventions in order to decrease the morbidity associated with surgical excision. AIM: This study aims to evaluate a novel approach that combines surgical excision with perilesional interferon injection in a pilot study. METHOD: A total of 23 patients with facial nodular/solid BCC were enrolled and randomised to receive surgical removal with frozen-section control followed by a single perilesional infiltration of either interferon-alpha or Ringer's lactate. Patients were evaluated for signs of local complications and recurrence after a minimal follow-up of 1 year. RESULTS AND CONCLUSION: No major complications occurred after infiltration of interferon. One patient required oral antibiotics in the interferon group and two patients showed a small wound dehiscence. At the 1-year follow-up, one patient suffered from a recurrence in the control group. No recurrence was observed in the interferon group. A single perilesional infiltration of interferon-alpha was safe and did not increase the local complication rate. No recurrence was observed. A larger study is required to analyse the potential of this combination approach in order to minimise the

safety margin and thereby decrease the morbidity associated with surgery while improving the cure rate.

[797]

**TÍTULO / TITLE:** - Folic acid prevents the initial occurrence of sporadic colorectal adenoma in Chinese over 50 years of age: a randomized clinical trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Prev Res (Phila). 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1158/1940-6207.CAPR-13-0013](#)

**AUTORES / AUTHORS:** - Fang JY; Gao QY; Chen HM; Chen Y; Wang Y; Wang ZH; Tang J; Ge ZZ; Chen XY; Sheng JQ; Fang DC; Yu CG; Zheng P

**INSTITUCIÓN / INSTITUTION:** - 1Shanghai Institute of Digestive, Division of Gastroenterology and Hepatology, Renji Hospital, Shanghai Jiao-Tong University School of Medicine.

**RESUMEN / SUMMARY:** - Colorectal adenoma (CRA) is the precursor lesion of colorectal cancer (CRC). Several agents have been shown to be effective in the chemoprevention of CRA recurrence, but there has been little research on its primary prevention. Participants aged >50 years with no adenomas were recruited for our study and randomized to receive either 1 mg/d FA supplement or treatment without FA. After 3 years of follow-up, plasma folate and colonoscopy were evaluated. Seven-hundred and ninety-one participants (91.98%) completed the study. CRA occurred in 64 (14.88%) participants in the FA group and 132 (30.70%) in the control group (unadjusted RR, 0.49; 95%CI: 0.37-0.63; P<0.01); left-sided adenoma (unadjusted RR, 0.54; 95%CI: 0.38-0.76; P=0.001) and advanced CRA (unadjusted RR, 0.36; 95%CI: 0.16-0.81; P=0.01) were most common. There was no significance difference in the occurrence of three or more adenomas (unadjusted RR, 0.70; 95%CI: 0.36-1.77; P=0.38) or right-sided adenoma (unadjusted RR, 0.55; 95%CI: 0.30-1.00; P=0.07) between the two groups. Participants with low plasma folate may had a high risk of CRA. In conclusion, primary prevention with 1mg/d FA supplementation could reduce the incidence of CRA, especially left-sided and advanced disease in those with no previous adenomas. People with differing baseline plasma folate levels should be given individualized treatment. Those with low plasma folate should be encouraged to take adequate supplements; plasma folate should be elevated to an effective therapeutic level, which may reduce the incidence of CRA.

[798]

**TÍTULO / TITLE:** - Interferon alfa in the treatment paradigm for non-muscle-invasive bladder cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Urol Oncol. 2013 Apr 26. pii: S1078-1439(13)00073-2. doi: 10.1016/j.urolonc.2013.02.010.

●●Enlace al texto completo (gratis o de pago)

[1016/j.urolonc.2013.02.010](http://1016/j.urolonc.2013.02.010)

**AUTORES / AUTHORS:** - Lamm D; Brausi M; O'Donnell MA; Witjes JA

**INSTITUCIÓN / INSTITUTION:** - BCG Oncology, P.C., Phoenix, AZ. Electronic address: [damm@bcgoncology.com](mailto:damm@bcgoncology.com).

**RESUMEN / SUMMARY:** - OBJECTIVES: In this article, we review the various options for and the potential role of interferon alfa (IFN-alpha) in the treatment of non-muscle-invasive bladder cancer (NMIBC). METHODS: PubMed was searched for journal articles on IFN-alpha use in treating bladder cancer. The references listed in the National Comprehensive Cancer Network guidelines were used as a guide to identify relevant publications on treatments for NMIBC. RESULTS: Transurethral resection with adjuvant intravesical chemotherapy or immunotherapy is the standard treatment option for NMIBC. Adjuvant IFN-alpha therapy has limited efficacy in preventing recurrences in intermediate-risk and high-risk patients; bacillus Calmette-Guerin (BCG) monotherapy is the recommended first-line treatment in these patients. Unfortunately, cancer progression or recurrence is a common outcome; radical cystectomy, which is often the lifesaving approach in such a scenario, is associated with significant morbidity, mortality, and decreased quality of life. Current alternatives to cystectomy include repeat intravesical immunotherapy, conventional instillation chemotherapy, and device-assisted intravesical chemotherapy. The efficacy of any chemotherapy after BCG failure, either conventional or device assisted, has not been established. BCG and IFN-alpha combination intravesical therapy has not been investigated thoroughly; based on available data, combination therapy appears to be most effective in patients with carcinoma in situ and may be preferentially considered as an alternative to radical cystectomy for patients with intermediate-risk or high-risk NMIBC who do not tolerate the standard BCG dose or experience BCG failure after 1 year of therapy. However, this approach requires close follow-up and should only be chosen after careful consideration of all risk factors. CONCLUSIONS: There is a lack of efficacious treatment options for patients with NMIBC recurrence or progression after initial BCG treatment. There is a need for well-designed clinical trials investigating the safety and efficacy of available therapies, including BCG and IFN-alpha2b combination therapy.

[799]

**TÍTULO / TITLE:** - Genetic polymorphisms of tumour necrosis factor alpha (TNF-alpha) promoter gene and response to TNF-alpha inhibitors in Spanish patients with inflammatory bowel disease.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Immunogenet. 2013 Apr 17. doi: 10.1111/iji.12059.

●●Enlace al texto completo (gratis o de pago) [1111/iji.12059](http://1111/iji.12059)

**AUTORES / AUTHORS:** - Lopez-Hernandez R; Valdes M; Campillo JA; Martinez-Garcia P; Salama H; Salgado G; Boix F; Moya-Quiles MR; Minguela A; Sanchez-Torres A; Miras M; Garcia A; Carballo F; Alvarez-Lopez MR; Muro M

**INSTITUCIÓN / INSTITUTION:** - Immunology Service, University Hospital Virgen de la Arrixaca, Murcia, España.

**RESUMEN / SUMMARY:** - Tumour necrosis factor alpha (TNF-alpha) has an important role in inflammatory response. Alterations in the regulation of TNF-alpha have been implicated in a variety of inflammatory disorders, including Inflammatory bowel disease (IBD). Indeed, a common treatment for IBD is the use of TNF-alpha inhibitors. Polymorphisms in the TNF-alpha promoter region are known to affect the level of gene expression. Our aim was to investigate the influence of these single nucleotide polymorphisms (SNPs) in TNF-alpha promoter gene play in the risk of IBD in a Spanish population and their individual response to anti-TNF-alpha treatment. DNA samples from patients with IBD and controls were screened for TNF-alpha -238G/A (rs361525) and -308G/A (rs1800629) SNPs by PCR-SSOP using a microbeads luminex assay and compared with response to TNF-alpha inhibitors. There were not statistical differences in -238G/A and -308G/A allele and genotype frequencies between patients. However, we found an increased frequency of -308A allele and -308GA genotype in these nonresponders patients to TNF-alpha inhibitors with respect to responders patients ( $P < 0.05$ ). This -308GA genotype has been classified as high producer of this cytokine. This fact could actually be interesting to explain the different response of patients with IBD with respect to TNF-alpha inhibitors. TNF-alpha promoter gene polymorphism does not seem to play a role in IBD susceptibility, but particular TNF-alpha genotypes may be involved in the different responses to TNF-alpha inhibitor treatment in Spanish patients with IBD.

[800]

**TÍTULO / TITLE:** - Profilin 1: do we have a novel proteome-found biomarker predicting response to anti-cancer therapy?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proteomics. 2013 May 15. doi: 10.1002/pmic.201300165.

●●Enlace al texto completo (gratis o de pago) [1002/pmic.201300165](http://1002/pmic.201300165)

**AUTORES / AUTHORS:** - Skvortsova I

**INSTITUCIÓN / INSTITUTION:** - Laboratory for Translational Research on Radiation Oncology, Dept. of Therapeutic Radiology and Oncology, Innsbruck Medical University, Austria.

**RESUMEN / SUMMARY:** - About three decades ago, profilin 1 was described as a 15 kDa small protein. It was later shown that profilin 1 is a tumor suppressor in human carcinomas. Recent proteome based data additionally demonstrated that the levels of profilin 1 expression could help to predict malignant tumor

aggressiveness, response to anti-cancer therapy and risk of recurrence development. This article is protected by copyright. All rights reserved.

[801]

**TÍTULO / TITLE:** - Acyl-CoA thioesterase 8 is a specific protein related to nodal metastasis and prognosis of lung adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathol Res Pract. 2013 May;209(5):276-83. doi: 10.1016/j.prp.2013.02.008. Epub 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago) [1016/j.prp.2013.02.008](#)

**AUTORES / AUTHORS:** - Jung WY; Kim YH; Ryu YJ; Kim BH; Shin BK; Kim A; Kim HK

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Korea University College of Medicine, Seoul, South Korea.

**RESUMEN / SUMMARY:** - Metastasis is a major cause of cancer recurrence or death. This study attempted to quantitatively identify different proteins in metastatic lung adenocarcinoma. The N/T quotient [number of metastatic lymph nodes (n)/tumor diameter (cm)] was used to select samples with an extreme metastatic phenotype. Among the six fresh frozen lung adenocarcinoma specimens, the three showing the highest N/T quotient represented the metastatic group, and others with the greatest tumor diameters without metastasis represented the non-metastatic group. After 2-dimensional electrophoresis, the significantly different protein spots were selected by image analysis and analyzed with MALDI-TOF mass spectrometry. Acyl-CoA thioesterase 8 isoform c (ACOT8) was one of most overexpressed proteins in the metastatic group, and it was validated by Western blot and immunohistochemical staining on 108 paraffin-embedded tumor samples. High ACOT8 expression was correlated with lymph node metastasis ( $p=0.002$ ), recurrence ( $p=0.034$ ), predominant histologic subtypes ( $p=0.007$ ), and higher stage ( $p=0.005$ ). In multivariate analysis, high ACOT8 expression was significantly associated with increased risks of lymph node metastasis ( $p=0.009$ ) and cancer-related death ( $p=0.030$ ), independent of clinical factors. ACOT8 may be a candidate prognostic biomarker and therapeutic target of lung adenocarcinoma.

[802]

**TÍTULO / TITLE:** - Oral carcinoma with perineural invasion has higher nerve growth factor expression and worse prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Dis. 2013 Mar 10. doi: 10.1111/odi.12101.

●●Enlace al texto completo (gratis o de pago) [1111/odi.12101](#)

**AUTORES / AUTHORS:** - Yu EH; Lui MT; Tu HF; Wu CH; Lo WL; Yang CC; Chang KW; Kao SY

**INSTITUCIÓN / INSTITUTION:** - Department of Dentistry, School of Dentistry, National Yang-Ming University, Taipei, Taiwan; Department of Dentistry, National Yang-Ming University Hospital, Yi-Lan, Taiwan.

**RESUMEN / SUMMARY:** - **BACKGROUND:** This study elucidated the association between histopathological factors and the prognosis of oral carcinoma. As the histopathological factors were determined from the surgical specimen and this can only be used for the choices of postoperative regimens, this study also investigated the linkage between prognostic factors and the expression of key molecules to examine the feasibility of markers as predictors. **METHODS:** Clinicopathological factors of 101 oral carcinomas were cross-analyzed with disease-free survival. The expression of nerve growth factor (NGF) and its receptor, tyrosine kinase A receptor, was assayed with immunohistochemistry. **RESULTS:** Nodal metastasis was the most crucial clinical predictor for disease-free survival. Perineural invasion (PNI) was an independent histopathological predictor for both nodal metastasis ( $P = 0.004$ ) and disease-free survival ( $P = 0.019$ ). Patients with advanced tumor and PNI exhibited the high hazard for tumor progression and poor disease-free survival. NGF immunoreactivity in tumors was correlated with PNI ( $P = 0.005$ ) and neck lymph node metastasis ( $P = 0.036$ ). **CONCLUSION:** Perineural invasion is the indicator of worst prognosis. As NGF immunoreactivity was found to be associated with PNI and nodal metastasis, the NGF immunoreactivity of oral carcinoma revealed by diagnostic biopsy suggests that alternative therapeutic approaches might be appropriate.

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[803]

**TÍTULO / TITLE:** - Effect of hepatitis B virus infection on apoptosis of a human choriocarcinoma cell line in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Obstet Gynaecol Res. 2013 Jun;39(6):1200-11. doi: 10.1111/jog.12046. Epub 2013 May 30.

●●Enlace al texto completo (gratis o de pago) [1111/jog.12046](#)

**AUTORES / AUTHORS:** - Bai G; Fu F; Tang Y; Wang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Gynecology and Obstetrics, The First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, China.

**RESUMEN / SUMMARY:** - **AIM:** To investigate the effect and mechanism of hepatitis B virus (HBV) infection on the human choriocarcinoma cell line, JEG-3, in relation to apoptosis and intrauterine infection. **MATERIAL AND METHODS:** HBV-DNA serum was used to infect the choriocarcinoma cell line, JEG-3, in vitro. Real-time fluorescence quantitative PCR (RT-PCR) was then employed to detect intracellular replication of HBV DNA. Cells were also stained with

Annexin-V and propidium iodide (PI) to identify the stages of apoptosis following infection. In addition, reverse transcription PCR was used to detect intracellular HBx mRNA levels, and Western blotting and immunohistochemistry were used to detect changes in the intracellular expression of HBxAg and phosphatidylinositol kinase 3 (PI3K). Flow cytometry was also used to detect the intracellular levels of phosphorylated AKT (pAKT). RESULTS: After JEG-3 cells were infected with HBV in vitro, HBV DNA was detected. The percentage of cells in early and late stage apoptosis also decreased significantly. Expression of HBx mRNA and HBxAg were detected, and intracellular levels of PI3K and pAKT were observed to significantly increase. CONCLUSION: HBV infected JEG-3 cells in vitro, resulting in an inhibition of early and late stage apoptosis. In addition, the HBxAg/PI3K/pAKT pathway is a possible mechanism mediating this inhibition of apoptosis, and the infection of the placenta by HBV.

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[804]

**TÍTULO / TITLE:** - Cytotoxicity of etoposide in cancer cell lines in vitro after BCL-2 and C-RAF gene silencing with antisense oligonucleotides.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Pol Pharm. 2013 Jan-Feb;70(1):87-97.

**AUTORES / AUTHORS:** - Sypniewski D; Bednarek I; Galka S; Loch T; Blaszczyk D; Soltysik D

**INSTITUCIÓN / INSTITUTION:** - Department of Biotechnology and Genetic Engineering, Medical University of Silesia in Katowice, Narcyzow 1, 41-200 Sosnowiec, Poland. [dsypniewski@sum.edu.pl](mailto:dsypniewski@sum.edu.pl)

**RESUMEN / SUMMARY:** - BCL-2 and C-RAF genes are overexpressed in most types of cancers. Although these genes are mediators in different molecular pathways their main characteristic is the antiapoptotic activity, thus cells that overexpress either BCL-2 or C-RAF lose their ability to undergo apoptotic death being resistant to chemotherapeutic agents and/or physiologic mediators of cell death (e.g., TNF-alpha). Both anti-C-RAF, and anti-BCL-2 oligonucleotides were tested as chemosensitizers in cancer therapy. The aim of the study was to investigate the effects of the combined use of antisense oligonucleotides (ASOs) targeting BCL-2 and C-RAF transcripts on the in vitro cancer cell cultures exposed to etoposide. Cells were transfected with phosphorothioate BCL-2 and C-RAF ASOs. To sustain high intracellular level of ASOs, 3-day transfection was used, and it was followed by a single treatment with 20 microM etoposide for 5 h. The following cancer cell lines were tested: A549, HeLa, and T24. Sequence-specific decrease in BCL-2, and C-RAF mRNA levels were confirmed by real-time RT-PCR: after 1-day treatment mRNA levels decreased by 9-42% of the normal expression in cells treated with 50-1200 nM ASOs. Also, the induction of cell death in all transfected cultures in a concentration-dependent manner was confirmed by MTT assay, microscopic analysis of cell morphology, and the measurement of histone H3 expression.

Results also showed that both ASOs effectively potentiated etoposide-induced cytotoxicity; the strongest effects were obtained in A549 (lung cancer). This observation suggests that lower concentrations of both antisense oligonucleotides may be used, at least for this type of cancer, to obtain high efficiency of etoposide-induced cell death enhancement. Simultaneous use of two ASOs in 3-day treatment allows us to lower concentrations needed to obtain significant treatment results thus enabling to diminish sequence-unspecific toxicity.

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[805]

**TÍTULO / TITLE:** - Temozolomide modulated glioma proteome: Role of Interleukin-1 receptor associated kinase-4 (IRAK4) in chemosensitivity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proteomics. 2013 Apr 18. doi: 10.1002/pmic.201200261.

●●Enlace al texto completo (gratis o de pago) [1002/pmic.201200261](http://1002/pmic.201200261)

**AUTORES / AUTHORS:** - Kumar DM; Patil V; Ramachandran B; Nila MV; Dharmalingam K; Somasundaram K

**INSTITUCIÓN / INSTITUTION:** - Microbiology and Cell Biology, Indian Institute of Science, Bangalore, 560 012.

**RESUMEN / SUMMARY:** - The current treatment for glioblastoma (GBM) includes temozolomide (TMZ) chemotherapy, yet the mechanism of action of TMZ is not thoroughly understood. Here, we investigated the TMZ induced changes in the proteome of the glioma derived cell line (U251) by 2D-DIGE. We found 95 protein spots to be significantly altered in their expression after TMZ treatment. Mass spectrometry identified four up-regulated spots: aspartyl tRNA synthetase (DARS) glutathione synthetase (GSS), interleukin-1 receptor associated kinase-4 (IRAK4), and breast carcinoma amplified sequence-1 (BCAS1) and one down-regulated spot: optineurin (OPTN). TMZ induced regulation of these five genes was validated by RT-qPCR and western blot analysis. RNAi mediated knockdown of IRAK4, an important mediator of Toll-like receptors (TLR) signaling and chemoresistance, rendered the glioma cells resistant to TMZ. High levels of IRAK4 induced upon TMZ treatment resulted in IRAK1 downregulation and inhibition of NFkB pathway. Endogenous IRAK4 protein, but not transcript levels in glioma cell lines, correlated with TMZ sensitivity. Thus we have identified several TMZ modulated proteins and discovered an important novel role for IRAK4 in determining TMZ sensitivity of glioma cells through its ability to inhibit TLR signaling and NFkB pathway This article is protected by copyright. All rights reserved.

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[806]

**TÍTULO / TITLE:** - Impact of interleukin-10, soluble CD25 and interferon-gamma on the prognosis and early diagnosis of bacteremic systemic inflammatory response syndrome: a prospective observational study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Crit Care. 2013 Apr 5;17(2):R64.

●●Enlace al texto completo (gratis o de pago) [1186/cc12596](#)

**AUTORES / AUTHORS:** - Matera G; Puccio R; Giancotti A; Quirino A; Pulicari MC; Zicca E; Caroleo S; Renzulli A; Liberto MC; Foca A

**INSTITUCIÓN / INSTITUTION:** - Institute of Microbiology, Department of Health Sciences, "Magna Graecia" University of Catanzaro, Viale Europa, 88100, Catanzaro, Italy. [gm4106@gmail.com](mailto:gm4106@gmail.com).

**RESUMEN / SUMMARY:** - INTRODUCTION: The pathophysiology of sepsis consists of two phases. A first phase characterized by a substantial increase of pro-inflammatory mediators including cytokines and systemic inflammatory markers, and a second phase (immunoparalysis, immunodysregulation) associated with the rise of anti-inflammatory mediators. In this study we prospectively analyzed 52 consecutive patients with diagnosis of systemic inflammatory response syndrome (SIRS) at hospital admission to evaluate prognostic and early diagnostic performance of interleukin-10 (IL-10), soluble CD25 (sCD25) and interferon-gamma (IFN-gamma) and to confirm the prognostic accuracy of the sequential organ failure assessment (SOFA) score. METHODS: Patients were divided in two groups (group 1, n = 28 patients with bacteremic SIRS and group 2, n = 24 patients with non-bacteremic SIRS) and then stratified into survivors (n = 39) and nonsurvivors (n = 13). Serum markers were evaluated on the day of hospital admission (D-1) and on the 7<sup>th</sup> day of hospital stay (D-7). Concentration of sCD25 was evaluated by a sandwich ELISA kit. Levels of IL-10 and IFN-gamma were quantified by a cytokine biochip array by the evidence investigator analyzer. Differences between groups were established by the Mann-Whitney test. Accuracy, sensitivity and specificity of diagnostic markers were evaluated by the receiver-operating characteristic curve analysis. Multivariate analysis was carried out to evaluate whether studied biomarkers are independent predictors of poor outcome in prognosis, and of bacteremic SIRS in diagnosis. RESULTS: IL-10, sCD25 and SOFA scores of survivors and nonsurvivors were significantly different both at D-1 (P = 0.0014; P = 0.014 and P = 0.0311 respectively) and at D-7 (P = 0.0002, P = 0.014 and P = 0.0012 respectively). Between the above groups IFN-gamma level was significantly different only at D-7 (P = 0.0013). Moreover IL-10 and sCD25 were significantly higher in bacteremic versus non-bacteremic SIRS patients at D-1 and at D-7 (P < 0.05). IFN-gamma values showed a significant decrease (P < 0.05) in patients of group 1 only at D-7. The diagnostic accuracy of IL-10 and sCD25 was confirmed by the analysis of the AUROCC at D-1 and D-7 respectively. Multivariate analysis revealed that sCD25 and IL-10 are independent predictors of a poor outcome for our patients during the first day of hospital admission. CONCLUSIONS: IL-10 and sCD25 gave a significant

contribution to prognostic evaluation and early diagnosis of bacteremic SIRS. SOFA score appeared to be a reliable prognostic tool in this subset of patients.

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[807]

**TÍTULO / TITLE:** - Imatinib and prostate cancer: lessons learned from targeting the platelet-derived growth factor receptor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Investig Drugs. 2013 Jun;22(6):787-94. doi: 10.1517/13543784.2013.787409. Epub 2013 Apr 1.

●●Enlace al texto completo (gratis o de pago)

[1517/13543784.2013.787409](#)

**AUTORES / AUTHORS:** - Rosenberg A; Mathew P

**INSTITUCIÓN / INSTITUTION:** - Tufts Medical Center, Department of Hematology and Oncology , 800 Washington St, Boston, MA 02111 , USA.

**RESUMEN / SUMMARY:** - Introduction: The platelet derived growth factor (PDGF) signaling pathway has been implicated in both epithelial and stromal mechanisms of prostate cancer progression and postulated as a target for therapy in bone metastases. Imatinib mesylate is a potent inhibitor of the platelet-derived growth factor receptor (PDGFR) and its activity has been tested in preclinical models and in Phase I and II clinical trials. Areas covered: This review summarizes the preclinical data on PDGF/PDGFR in prostate cancer, and reviews the clinical and correlative data using imatinib as a PDGFR inhibitor. Expert opinion: To date, the use of imatinib to treat men with prostate cancer has been ineffective, and PDGFR inhibition may in fact accelerate advanced forms of the disease and antagonize taxane efficacy. Given the major discordance between preclinical models and clinical experimentation, an accurate understanding of the PDGF-regulated interactions between metastatic prostate cancer and the bone micro-environment is evidently warranted. Correlations of pharmacodynamic monitoring of imatinib-induced PDGFR inhibition with progression-free and overall survival outcomes have led to the hypothesis that PDGF may function as a homeostatic factor in bone metastases. Recent laboratory studies defining PDGFR-regulated pericytes as gatekeepers of metastases may relate to these clinical observations.

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[808]

**TÍTULO / TITLE:** - MicroRNAs and Cancer: Towards a Personalized Medicine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Mol Med. 2013 Jun 1;13(5):751-6.

**AUTORES / AUTHORS:** - Fabbri M

**INSTITUCIÓN / INSTITUTION:** - Children's Hospital Los Angeles, 4650 Sunset Blvd, Mailstop #57, Los Angeles, CA 90027, USA. [mfabbri@chla.usc.edu](mailto:mfabbri@chla.usc.edu).

**RESUMEN / SUMMARY:** - MicroRNAs (miRNAs) are de-regulated in cancer versus the normal tissue counterpart and actively participate in human carcinogenesis. Among the genes whose expression is under their control there are both oncogenes and tumor suppressor genes, revealing that it is not only limiting but simply wrong to assign them a function just as oncogenes or as tumor suppressor genes. In addition to primary tumors, miRNAs can be detected in almost all human body fluids and effectively help to diagnose cancer and to prognosticate clinical outcome and response to treatment of tumors. The advent of miRNA mimic and miRNA silencing molecules has allowed to modulate miRNA expression in tumors, showing that miRNAs can be effectively used as therapeutic agents. This review will focus on those findings that have provided the rationale for the use of miRNAs as patient “tailored” anti-cancer agents.

[809]

**TÍTULO / TITLE:** - Pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios do not predict survival in patients with cervical cancer treated with neoadjuvant chemotherapy and radical hysterectomy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin Med J (Engl). 2013 Apr;126(8):1464-8.

**AUTORES / AUTHORS:** - Wang D; Wu M; Feng FZ; Huang HF; Yang JX; Shen K; Xiang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China.

**RESUMEN / SUMMARY:** - BACKGROUND: A few inflammatory markers were studied to evaluate their possible prognostic roles in various cancers. The neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are hypothesized to reflect the systemic inflammation. The objective of the present study was to investigate whether or not the pretreatment neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio can predict the survival of patients with cervical cancer treated with neoadjuvant chemotherapy and radical hysterectomy. METHODS: We performed a retrospective study on cervical cancer patients (FIGO stage Ib2-IIb) who had undergone neoadjuvant chemotherapy and radical hysterectomy at Peking Union Medical College Hospital between January 1999 and December 2010. Data on demographics, clinical prognostic markers and histopathology were collected and analyzed. Univariate and multivariate analyses for prognostic factors were performed. RESULTS: A total of 111 patients were identified. The median neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were 2.4 and 142.2, respectively. Overall survival and progression-free survival were neither significantly different between patients with high and low neutrophil-to-lymphocyte ratio ( $P = 0.149$  and  $P = 0.108$ ) nor in high and low platelet-to-lymphocyte ratio ( $P = 0.336$  and  $P =$

0.510). On multivariate analysis, lymph node status ( $P = 0.000$  and  $P = 0.007$ ) and lymphovascular space involvement ( $P = 0.001$  and  $P = 0.001$ ) were independent prognostic factors of progression-free survival and overall survival. CONCLUSIONS: Lymph node status and lymphovascular space involvement were found to be independent prognostic factors for patients with cervical cancer who underwent neoadjuvant chemotherapy and radical hysterectomy. The pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios seemed not to predict the survival of patients with cervical cancer treated with neoadjuvant chemotherapy and radical hysterectomy.

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[810]

**TÍTULO / TITLE:** - BRAF(V600E) mutation is a negative prognosticator in pediatric ganglioglioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Neuropathol. 2013 Jun;125(6):901-10. doi: 10.1007/s00401-013-1120-y. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1007/s00401-013-1120-y](#)

**AUTORES / AUTHORS:** - Dahiya S; Haydon DH; Alvarado D; Gurnett CA; Gutmann DH; Leonard JR

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA.

**RESUMEN / SUMMARY:** - Gangliogliomas are typically low-grade neuroepithelial tumors seen in the pediatric and young adult populations. Despite their often bland histologic appearance, these tumors recur with varying frequencies; however, little data exist that adequately predict ganglioglioma recurrence in children. To identify potential histopathologic features predictive of recurrence-free survival, a series of 53 patients with World Health Organization (WHO) grade I gangliogliomas were evaluated, representing the largest cohort of pediatric gangliogliomas with accompanying histopathologic and survival data. Fifteen patients (28 %) exhibited disease recurrence during the study period. BRAF(V600E) immunohistochemistry was performed on 47 of these tumors. Histopathologic features associated with shorter recurrence-free survival included an absence of oligodendroglial morphology, higher glial cell density, microvascular proliferation, and the presence of a high lymphoplasmacytic inflammatory infiltrate. Eighteen tumors (38.3 %) had positive BRAF(V600E) staining, which was associated with shorter recurrence-free survival. Collectively, the combined use of histopathologic and molecular features to stratify grade I gangliogliomas into low and high-risk groups provides important information relevant to the management of children and young adults with these rare tumors.

[811]

**TÍTULO / TITLE:** - Infections associated with the use of tumor necrosis factor-alpha inhibitors in psoriasis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Drugs Dermatol. 2013 Mar;12(3):e41-5.

**AUTORES / AUTHORS:** - Tan X; Balkrishnan R; Feldman SR

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA. [tanxi@umich.edu](mailto:tanxi@umich.edu)

**RESUMEN / SUMMARY:** - Tumor necrosis factor (TNF)-alpha inhibitors have been shown to increase the risks of overall infection and serious infection in rheumatoid arthritis. However, it is uncertain whether we can draw the same conclusion in the psoriatic population. This article focuses on the 3 most commonly used TNF-alpha inhibitors in psoriasis: adalimumab, etanercept, and infliximab. In order to assess the risks of overall infection and serious infection in patients with psoriasis, we reviewed the underlying mechanism of the potential infection risk, different types of serious infection associated with TNF-alpha inhibitors, and current evidence in the psoriatic population. Results from 11 randomized controlled trials and open-label extension studies showed that there was no apparent significant association between the use of TNF-alpha inhibitors and increasing risks of overall infection and serious infection. Because of the limitations of current evidence, large, long-term follow-up studies with appropriate control groups using real-life data, such as postmarket surveillance, are warranted.

[812]

**TÍTULO / TITLE:** - Polymorphisms in thymidylate synthase and reduced folate carrier ( ) genes predict survival outcome in advanced non-small cell lung cancer patients treated with pemetrexed-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1165-1170. Epub 2013 Feb 4.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1175](#)

**AUTORES / AUTHORS:** - Li WJ; Jiang H; Fang XJ; Ye HL; Liu MH; Liu YW; Chen Q; Zhang L; Zhang JY; Yuan CL; Zhang QY

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The Second People's Hospital of Lianyungang (Lianyungang Hospital Affiliated to Bengbu Medical College), Jiangsu 222000, P.R. China.

**RESUMEN / SUMMARY:** - The aim of this study was to evaluate the association between thymidylate synthase (TS), methylenetetrahydrofolate reductase (MTHFR) and reduced folate carrier (SLC19A1) gene polymorphisms and the treatment efficacy of pemetrexed-based chemotherapy in advanced non-small cell lung cancer (NSCLC). Advanced NSCLC patients received pemetrexed and cisplatin every three weeks. Polymorphisms in the TS, MTHFR and SLC19A1 genes were detected in peripheral blood samples using DNA sequencing and

Taqman PCR. An analysis of gene polymorphisms was performed with respect to the progression-free survival (PFS), response rate (RR) and overall survival (OS) of patients treated with pemetrexed. The median PFS times for patients with the TS 2R/2R, 2R/3C or 3C/3C genotypes were significantly longer than those of patients with the 2R/3G, 3C/3G or 3G/3G genotypes (P=0.036). Patients with the SLC19A1 CC genotype had a significantly longer median OS compared with individuals with the homozygous and heterozygous genotypes (12.2 vs. 8.9 and 7.3 months, respectively; P=0.022). The PFS and OS did not differ for the three genotypes of MTHFR assessed. The RR was higher in patients with the TS 2R/2R, 2R/3C or 3C/3C genotypes than in the other groups (P=0.044). The polymorphisms of the 5'-UTR of the TS gene and exon 6 (2522) C/T of the SLC19A1 gene predict the survival of advanced NSCLC patients treated with pemetrexed. However, a large scale clinical trial is required to validate these findings.

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[813]

**TÍTULO / TITLE:** - SNPs in microRNA binding sites as prognostic and predictive cancer biomarkers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Crit Rev Oncog. 2013;18(4):327-40.

**AUTORES / AUTHORS:** - Preskill C; Weidhaas JB

**INSTITUCIÓN / INSTITUTION:** - Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, USA.

**RESUMEN / SUMMARY:** - Single-nucleotide polymorphisms within microRNA (miRNA) binding sites comprise a novel genre of cancer biomarkers. Since miRNA regulation is dependent on sequence complementarity between the mRNA transcript and the miRNA, even single-nucleotide aberrations can have significant effects. Over the past few years, many examples of these functional miRNA binding site SNPs have been identified as cancer biomarkers. While most of the research to date focuses on associations with cancer risk, more and more studies are linking these SNPs to cancer prognosis and response to treatment as well. This review summarizes the state of the field and draws importance to this rapidly expanding area of cancer biomarkers.

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[814]

**TÍTULO / TITLE:** - MicroRNAs as new diagnostic and prognostic biomarkers in urological tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Crit Rev Oncog. 2013;18(4):289-302.

**AUTORES / AUTHORS:** - Fendler A; Jung K

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Charite - University Medicine and Berlin Institute for Urological Research, Berlin, Germany.

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**RESUMEN / SUMMARY:** - MicroRNAs are single-stranded regulatory molecules that play an important role during carcinogenesis. Since microRNA expressions are deregulated in cancer and they have proven to be very stable in clinical specimens, they have become attractive molecules as markers for the diagnosis and prognosis, as well as for prediction of therapy response and surveillance, of cancer. In this review, we summarize the latest findings on microRNAs in tissue and body fluids of patients suffering from urological tumors and their utilization as noninvasive or tissue markers for detection and stratification of these tumors.

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[815]

**TÍTULO / TITLE:** - Prognostic value of human papillomavirus types 16 and 18 DNA physical status in cervical intraepithelial neoplasia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Microbiol Infect. 2013 Mar 27. doi: 10.1111/1469-0691.12233.

●●Enlace al texto completo (gratis o de pago) [1111/1469-0691.12233](http://1111/1469-0691.12233)

**AUTORES / AUTHORS:** - Gradissimo Oliveira A; Delgado C; Verdasca N; Pista A

**INSTITUCIÓN / INSTITUTION:** - National Reference Laboratory of STI for Human Papillomavirus and Genital Herpes Virus, Department of Infectious Diseases, National Institute of Health, Lisbon, Portugal.

**RESUMEN / SUMMARY:** - The aim of this work was to assess the value of the physical status of human papillomavirus (HPV) DNA as a disease marker for cervical cancer development in a set of 248 DNA samples previously genotyped as HPV 16 or 18, by calculating the E2/E6 ratio through real-time PCR. There was a significant difference in integration status according to disease grade for both genotypes ( $p < 0.001$ ). Furthermore, especially for HPV 18, determining the DNA physical status could be a useful biomarker in predicting cervical cancer risk development, with a lower E2/E6 ratio clinically associated with the development of a precancerous lesion.

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[816]

**TÍTULO / TITLE:** - Is Alpha-B Crystallin an Independent Marker for Prognosis in Lung Cancer?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Heart Lung Circ. 2013 Apr 9. pii: S1443-9506(13)00037-1. doi: 10.1016/j.hlc.2013.01.014.

●●Enlace al texto completo (gratis o de pago) [1016/j.hlc.2013.01.014](http://1016/j.hlc.2013.01.014)

**AUTORES / AUTHORS:** - Campbell-Lloyd AJ; Mundy J; Deva R; Lampe G; Hawley C; Boyle G; Griffin R; Thompson C; Shah P

**INSTITUCIÓN / INSTITUTION:** - Princess Alexandra Hospital, Australia.

**RESUMEN / SUMMARY:** - BACKGROUND: Alpha B-crystallin (CRYAB) is an oncogene that increases tumour survival by promoting angiogenesis and preventing apoptosis. CRYAB is an independent prognostic marker in epithelial tumours including head and neck squamous cell carcinoma and breast cancer where it is predictive of nodal status and associated with poor outcome. We explored the role of CRYAB in non-small-cell lung cancer (NSCLC). METHODS: Immunohistochemical analysis was performed on 50 samples. Following staining with anti-alpha-B crystallin antibody, a blinded pathologist scored samples for nuclear (N) and cytoplasmic © staining intensity. Analysis was performed using Cox's proportional hazards model. RESULTS: There were 32 adenocarcinomas and 18 squamous cell carcinomas. The median tumour size was T2, grade 2 moderately differentiated, and 10 patients had nodal spread. Recurrence was seen in 22 patients (46%). Mortality was 48%, with median time to mortality 871 days. N staining was detected in eight samples (16%), and C staining in 20 (40%), with both N and C staining positive in five (10%). Staining for CRYAB predicted neither recurrence (N stain p=0.78, C stain p=0.38) nor mortality (N stain p=0.86, C stain p=0.66). CONCLUSION: CRYAB did not predict outcomes in patients treated for NSCLC. Larger studies are required to validate this finding.

[817]

**TÍTULO / TITLE:** - Simvastatin induced HCT116 colorectal cancer cell apoptosis through p38MAPK-p53-survivin signaling cascade.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 Apr 12;1830(8):4053-4064. doi: 10.1016/j.bbagen.2013.04.011.

●●Enlace al texto completo (gratis o de pago)

[1016/j.bbagen.2013.04.011](#)

**AUTORES / AUTHORS:** - Chang HL; Chen CY; Hsu YF; Kuo WS; Ou G; Chiu PT; Huang YH; Hsu MJ

**INSTITUCIÓN / INSTITUTION:** - Division of General Surgery, Department of Surgery, Landseed Hospital, Taoyuan, Taiwan.

**RESUMEN / SUMMARY:** - BACKGROUND: Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors with cholesterol-lowering properties, were recently shown to exhibit anti-cancer effects. However, the molecular mechanism underlying statin-induced cancer cell death remains to be elucidated. Elevated level of survivin is often found over-expressed in human cancers and has been implicated in the progression of tumorigenesis. Given its central role in cell division and action as an apoptosis suppressor, survivin represents a potential molecular target in cancer management. METHODS: In this study, we explored the underlying mechanisms in simvastatin-induced HCT116 colorectal cancer cell apoptosis. RESULTS: Simvastatin decreased cell viability and induced cell apoptosis in HCT116 cells. These results are

associated with the modulation of p21cip/Waf1 and survivin. Survivin knockdown using survivin siRNAs also decreased cell viability and induced cell apoptosis. Simvastatin's actions on p21cip/Waf1, survivin and apoptosis were reduced in p53 null HCT116 cells. Simvastatin caused an increase in p53 phosphorylation and acetylation. In addition, simvastatin activated p38 mitogen-activated protein kinase (p38MAPK), whereas an inhibitor of p38MAPK signaling abrogated simvastatin's effects of increasing p53 and p21cip/Waf1 promoter luciferase activity. Cell viability and survivin promoter luciferase activity in the presence of simvastatin were also restored by p38MAPK inhibitor. Furthermore, Sp1 binding to the survivin promoter region decreased while p53 and p63 binding to the promoter region increased after simvastatin exposure. CONCLUSIONS: Simvastatin activates the p38MAPK-p53-survivin cascade to cause HCT116 colorectal cancer cell apoptosis. GENERAL SIGNIFICANCE: This study delineates, in part, the underlying mechanisms of simvastatin in decreasing survivin and subsequent colorectal cancer cell apoptosis.

[818]

**TÍTULO / TITLE:** - Phase II study assessing lapatinib added to letrozole in patients with progressive disease under aromatase inhibitor in metastatic breast cancer-Study BES 06.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Target Oncol. 2013 Jun;8(2):137-43. doi: 10.1007/s11523-013-0279-4. Epub 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1007/s11523-013-0279-](#)

[4](#)

**AUTORES / AUTHORS:** - Villanueva C; Romieu G; Salvat J; Chaigneau L; Merrouche Y; N'guyen T; Vuillemin AT; Demarchi M; Dobi E; Pivot X

**INSTITUCIÓN / INSTITUTION:** - Centre Hospitalier Universitaire de Besancon, Besancon, France, [cvillanueva@chu-besancon.fr](mailto:cvillanueva@chu-besancon.fr).

**RESUMEN / SUMMARY:** - This trial evaluated the effect of adding lapatinib to letrozole after clinical resistance to aromatase inhibitor (IA) treatment in hormone receptor-positive metastatic breast cancer. Postmenopausal women received daily letrozole plus lapatinib (1,500 mg). The primary end point was objective rate response (ORR) at week 12. Secondary objectives included time to response, duration of response, clinical benefit (CB), progression-free survival (PFS), overall survival, and safety. Twenty-four human epidermal growth factor receptor 2 (HER2)-negative patients were included with secondary resistance to IA. ORR at 12 weeks was 4 % (95 % confidence interval (CI), 0.7-20). Stable and progression diseases were reported in 25 % (95 % CI, 12-45) and 71 % (95 % CI, 51-85) of cases, respectively. At 24 weeks, the ORR increased to 8 %. CB was 21 % (95 % CI, 9-40). At a median follow-up of 27 months, median PFS was 3.4 months (95 % CI, 2.8-5.4). Grade 3 or 4 adverse events were rarely reported. No clinical cardiac toxicity was

observed. Lapatinib was discontinued in two patients due to severe diarrhea. This trial was prematurely closed due to low recruitment. These preliminary results suggest that the addition of lapatinib to letrozole has a favorable safety profile and could overcome tumoral resistance to letrozole among HER2-negative tumors.

[819]

**TÍTULO / TITLE:** - The WHO score predicts treatment outcome in low risk gestational trophoblastic neoplasia patients treated with weekly intramuscular methotrexate.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer Res Ther. 2013 Jan-Mar;9(1):38-43. doi: 10.4103/0973-1482.110357.

●●Enlace al texto completo (gratis o de pago) [4103/0973-1482.110357](#)

**AUTORES / AUTHORS:** - Gilani MM; Fariba B; Behtash N; Ghaemmaghami F; Moosavi AS; Rezayof E

**INSTITUCIÓN / INSTITUTION:** - Department of Gynecology and Oncology, Tehran University of Medical Sciences, Valie Asr Hospital, Tehran; Department of Gynecology, Beheshti Hospital, Motahari street, Isfahan, Iran.

**RESUMEN / SUMMARY:** - BACKGROUND: Gestational trophoblastic neoplasia (GTN) includes a spectrum of disease ranging from hydatidiform mole to choriocarcinoma. Low risk GTN is defined as persistent molar pregnancy with a WHO score lower than seven. The optimal chemotherapeutic regimen still remains controversial. Aim: The objectives of this study was to determine efficacy and safety of weekly intramuscular methotrexate in the treatment of low risk gestational trophoblastic neoplasia (LRGTN) and also identify prognostic factors associated with treatment failure, necessitating second line chemotherapy. Materials and Methods: Sixty-six women with LRGTN from 2001 to 2009 were treated with weekly intramuscular methotrexate at 40 mg/m<sup>2</sup> as first line therapy. Monitoring of treatment was done with weekly checking of betaHCG level. Three consecutive negative betaHCG measurements showed complete response. After first negative betaHCG measurement, one additional dose was administered for consolidation. Results: Of 66 patients, who started the treatment five continued their treatment in other medical centres and were excluded from final analysis for treatment evaluation, and seven discontinued first line therapy because of hepatotoxicity. Of the remaining 54, complete remission occurred in 43 (79.6%) and eleven were resistant to first line therapy. Mean WHO score prior to starting chemotherapy was significantly different between two groups of response and resistance according to our data. Change of treatment to second line Actinomycin-D was necessary in eighteen cases because of resistance to first line in eleven and liver enzyme elevation in seven patients. Sixteen of these 18 responded to Actinomycin-D as second line and one needed hysterectomy for complete response. One patient received multiagent chemotherapy for complete remission. Conclusion: We recommend

this effective and safe method of chemotherapy for women with LRGTN. According to our data, lower mean WHO score predicts a better outcome for this regimen.

[820]

**TÍTULO / TITLE:** - A thienopyrimidine derivative induces growth inhibition and apoptosis in human cancer cell lines via inhibiting Aurora B kinase activity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 May 4;65C:151-157. doi: 10.1016/j.ejmech.2013.04.058.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ejmech.2013.04.058](#)

**AUTORES / AUTHORS:** - Li J; Hu H; Lang Q; Zhang H; Huang Q; Wu Y; Yu L

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Genetic Engineering, Institute of Genetics, School of Life Science, Fudan University, Shanghai 200433, PR China.

**RESUMEN / SUMMARY:** - Aurora kinases play a key role in the regulation of mitosis and have been regarded as promising targets of cancer therapy. In this paper we describe a thienopyrimidine derivative (S7), a novel potent ATP-competitive hit inhibitor of Aurora B kinase screened through a HTS system, with the IC<sub>50</sub> 141.12 nM in the biochemical kinase activity assay. Human tumor cells treated with S7 showed dose-dependent inhibition of auto-phosphorylation of Aurora B on Thr232 and another widely-used marker specific for Aurora B kinase, the phosphorylation of Histone H3 (Ser 10), demonstrating endogenous Aurora B kinase activity were inhibited at cellular level. Moreover, S7 treatment induced proliferation inhibition, colony formation inhibition and apoptosis of human tumor cell lines in a dose- and time-dependent manner.

[821]

**TÍTULO / TITLE:** - Neoadjuvant chemotherapy induces expression levels of breast cancer resistance protein that predict disease-free survival in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 2;8(5):e62766. doi: 10.1371/journal.pone.0062766. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062766](#)

**AUTORES / AUTHORS:** - Kim B; Fatayer H; Hanby AM; Horgan K; Perry SL; Valleley EM; Verghese ET; Williams BJ; Thorne JL; Hughes TA

**INSTITUCIÓN / INSTITUTION:** - Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom ; Department of Breast Surgery, Leeds General Infirmary, Leeds, United Kingdom.

**RESUMEN / SUMMARY:** - Three main xenobiotic efflux pumps have been implicated in modulating breast cancer chemotherapy responses. These are P-glycoprotein (Pgp), Multidrug Resistance-associated Protein 1 (MRP1), and Breast Cancer Resistance Protein (BCRP). We investigated expression of these proteins in breast cancers before and after neoadjuvant chemotherapy (NAC) to determine whether their levels define response to NAC or subsequent survival. Formalin-fixed paraffin-embedded tissues were collected representing matched pairs of core biopsy (pre-NAC) and surgical specimen (post-NAC) from 45 patients with invasive ductal carcinomas. NAC regimes were anthracyclines +/- taxanes. Immunohistochemistry was performed for Pgp, MRP1 and BCRP and expression was quantified objectively using computer-aided scoring. Pgp and MRP1 were significantly up-regulated after exposure to NAC (Wilcoxon signed-rank  $p = 0.0024$  and  $p < 0.0001$ ), while BCRP showed more variation in response to NAC, with frequent up- (59% of cases) and down-regulation (41%) contributing to a lack of significant difference overall. Pre-NAC expression of all markers, and post-NAC expression of Pgp and MRP1 did not correlate with NAC response or with disease-free survival (DFS). Post-NAC expression of BCRP did not correlate with NAC response, but correlated significantly with DFS (Log rank  $p = 0.007$ ), with longer DFS in patients with low post-NAC BCRP expression. In multivariate Cox regression analyses, post-NAC BCRP expression levels proved to predict DFS independently of standard prognostic factors, with high expression associated with a hazard ratio of 4.04 (95% confidence interval 1.3-12.2;  $p = 0.013$ ). We conclude that NAC-induced expression levels of BCRP predict survival after NAC for breast cancer, while Pgp and MRP1 expression have little predictive value.

[822]

**TÍTULO / TITLE:** - The prognostic significance of FOXQ1 oncogene overexpression in human hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathol Res Pract. 2013 Jun;209(6):353-8. doi: 10.1016/j.prp.2013.03.005. Epub 2013 Mar 25.

●●Enlace al texto completo (gratis o de pago) [1016/j.prp.2013.03.005](http://1016/j.prp.2013.03.005)

**AUTORES / AUTHORS:** - Wang W; He S; Ji J; Huang J; Zhang S; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Medical School of Nantong University, Nantong, China.

**RESUMEN / SUMMARY:** - FOXQ1 (forkhead box Q1) is a forkhead transcription factor, and FOX genes play significant roles in a series of biological processes. The aim of our study was to verify the importance of FOXQ1 as a prognostic indicator in HCC patients. One-step quantitative real-time PCR was performed to identify the expression of FOXQ1 mRNA in HCC and corresponding non-cancerous tissues. FOXQ1 expression was then evaluated by immunohistochemistry (IHC) using tissue microarray. Finally, we analyzed FOXQ1 expression and clinicopathological factors in 114 HCC patients using

SPSS 20.0 software. FOXQ1 expression at the transcriptional level in HCC cells was much higher than in the noncancerous cells ( $P=0.012$ , respectively). Comparison of clinicopathological characteristics and FOXQ1 expression in HCC by IHC and chi(2) tests showed that high FOXQ1 expression was linked to large tumor diameter, high serum alpha-fetoprotein levels and later stage grouping with tumor node metastasis classification. Kaplan-Meier and Cox regression analyses showed that high FOXQ1 expression and regional lymph node metastasis were independent prognostic factors. Our study demonstrates that an aggressive malignant phenotype of HCC is strongly linked to high FOXQ1 expression, and FOXQ1 may be a novel target in HCC therapy. Furthermore, it is likely that FOXQ1 is an oncogene in HCC.

[823]

**TÍTULO / TITLE:** - Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 May 12. pii: S0925-4439(13)00159-2. doi: 10.1016/j.bbadis.2013.05.005.

●●Enlace al texto completo (gratis o de pago)

[1016/j.bbadis.2013.05.005](#)

**AUTORES / AUTHORS:** - Pickard MR; Mourtada-Maarabouni M; Williams GT

**INSTITUCIÓN / INSTITUTION:** - Apoptosis Research Group, Institute of Science and Technology in Medicine, School of Life Sciences, Keele University, Huxley Building, Keele ST5 5BG, United Kingdom. Electronic address:

[m.r.pickard@keele.ac.uk](mailto:m.r.pickard@keele.ac.uk).

**RESUMEN / SUMMARY:** - While the role of small non-coding RNAs, such as miRNAs, in apoptosis control is well established, long non-coding RNAs (lncRNAs) have received less attention. Growth Arrest-Specific 5 (GAS5) encodes multiple snoRNAs within its introns, while exonic sequences produce lncRNA which can act as a riborepressor of the glucocorticoid and related receptors. GAS5 negatively regulates the survival of lymphoid and breast cells, and is aberrantly expressed in several cancers. Although cellular GAS5 levels decline as prostate cancer cells acquire castration-resistance, the influence of GAS5 on prostate cell survival has not been determined. To address this question, prostate cell lines were transfected with GAS5-encoding plasmids or GAS5 siRNAs, and cell survival was assessed. Basal apoptosis increased, and cell survival decreased, after transfection of 22Rv1 cells with plasmids encoding GAS5 transcripts, including mature GAS5 lncRNA alone. Similar effects were observed in PC-3 cells. In stable clones of 22Rv1, cell death correlated strongly with cellular GAS5 levels. Induction of 22Rv1 cell death by UV-C irradiation and chemotherapeutic drugs was augmented in cells transiently transfected with GAS5 constructs, and attenuated following down-regulation of GAS5 expression. Again, in these experiments, cell death was strongly correlated with

cellular GAS5 levels. Thus, GAS5 promotes the apoptosis of prostate cells, and exonic sequence, i.e. GAS5 lncRNA, is sufficient to mediate this activity. Abnormally low levels of GAS5 expression may therefore reduce the effectiveness of chemotherapeutic agents. Although several lncRNAs have recently been shown to control cell survival, this is the first report of a death-promoting lncRNA in prostate cells.

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[824]

**TÍTULO / TITLE:** - Axl and prostaticin are biomarkers for prognosis of ovarian adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Diagn Pathol. 2013 May 23. pii: S1092-9134(13)00035-X. doi: 10.1016/j.anndiagpath.2013.01.005.

●●Enlace al texto completo (gratis o de pago)

[1016/j.anndiagpath.2013.01.005](http://1016/j.anndiagpath.2013.01.005)

**AUTORES / AUTHORS:** - Chen PX; Li QY; Yang Z

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynaecology, Second Xiangya Hospital, Central South University, Changsha, Hunan, China.

**RESUMEN / SUMMARY:** - In this study, the protein levels of Axl and prostaticin in malignant neoplasms of the ovary and their clinicopathologic significance were investigated. The protein levels of Axl and prostaticin in ovarian adenocarcinomas (n = 80), serous cystadenoma (n = 15), mucinous cystadenomas (n = 15), and normal ovary tissues (n = 10) were measured using immunohistochemistry. The percentage of Axl-positive cases was significantly higher in ovarian adenocarcinoma (61.3%) than in mucinous adenoma tissues (13.3%; P < .001) and normal tissues (0.0%; P = .000). The percentage of prostaticin-positive cases was significantly lower in ovarian adenocarcinoma (42.5%) than in mucinous adenoma tissues (86.7%; P = .000) and normal tissues (100%; P = .000). The expression of Axl was significantly lower in cases with G1 tumor and TNM stage I or II tumor with no lymph node metastasis than in cases with G3 tumor and TNM stage III or IV tumor with lymph node metastasis (P < .05 or P < .01). However, the expression pattern of prostaticin was opposite to that of Axl (P < .01 or P < .01). Univariate Kaplan-Meier analysis showed a negative correlation between Axl expression (P = .000) and overall survival and a positive correlation between prostaticin expression (P = .000) and overall survival. Multivariate Cox regression analysis showed that Axl-positive expression and prostaticin-negative expression are independent bad prognostic predictors in ovarian adenocarcinoma. Our study suggested that Axl and prostaticin expression may be closely related to carcinogenesis, metastasis, and prognosis of ovarian adenocarcinoma.

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[825]

**TÍTULO / TITLE:** - NF-kappaB Inhibition by Bortezomib Permits Interferon-gamma-Activated RIP1 Kinase-Dependent Necrosis in Renal Cell Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 8.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1010](#)

**AUTORES / AUTHORS:** - Thapa RJ; Chen P; Cheung M; Nogusa S; Pei J; Peri S; Testa JR; Balachandran S

**INSTITUCIÓN / INSTITUTION:** - Immune Cell Development and Host Defense Program, Fox Chase Cancer Center.

**RESUMEN / SUMMARY:** - Advanced renal cell carcinoma (RCC) is an invariably fatal cancer. Currently, small-molecule inhibitors that target cell-growth, angiogenesis, or nutrient-sensing pathways represent the primary pharmacological interventions for this disease, but these inhibitors only delay tumor progression and are not curative. The cytokine interferon (IFN)-gamma showed the potential to provide lasting remission in several phase I/II trials for advanced RCC, but subsequent trials, including a multi-center phase III study using IFN-gamma as a monotherapy for RCC, were less promising. Notably, these trials were designed to exploit the indirect immune-modulatory effects of IFN-gamma, while its direct anti-tumor properties - including its ability to trigger programmed cell death in tumors - remain mostly untapped. Here, we show that the proteasome inhibitor bortezomib (PS-341, Velcade) sensitizes otherwise-resistant RCC cells to direct necrotic death by IFN-gamma. Mechanistically, we demonstrate that bortezomib functions at least in part by inhibiting pro-survival NF-kappaB signaling. In the absence of this signal, IFN-gamma triggers programmed necrosis (or 'necroptosis') dependent on the kinase RIP1. When taken together with the observation that NF-kappaB signaling is elevated in RCC, these results provide rationale for the combined use of IFN-gamma and bortezomib in the treatment of metastatic RCC.

[826]

**TÍTULO / TITLE:** - Phosphoproteomics data classify hematological cancer cell lines according to tumor type and sensitivity to kinase inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genome Biol. 2013 Apr 29;14(4):R37.

●●Enlace al texto completo (gratis o de pago) [1186/gb-2013-14-4-r37](#)

**AUTORES / AUTHORS:** - Casado P; Alcolea MP; Iorio F; Rodriguez-Prados JC; Vanhaesebroeck B; Saez-Rodriguez J; Joel S; Cutillas PR

**INSTITUCIÓN / INSTITUTION:** - Analytical Signalling Group, Centre for Cell Signalling, Barts Cancer Institute, Queen Mary University of London, Charterhouse Square, London EC1B 6BQ, UK. [pedro.cutillas@imperial.ac.uk](mailto:pedro.cutillas@imperial.ac.uk).

**RESUMEN / SUMMARY:** - BACKGROUND: Tumor classification based on their predicted responses to kinase inhibitors is a major goal for advancing targeted

personalized therapies. Here, we used a phosphoproteomic approach to investigate biological heterogeneity across hematological cancer cell lines including acute myeloid leukemia, lymphoma, and multiple myeloma. RESULTS: Mass spectrometry was used to quantify 2,000 phosphorylation sites across three acute myeloid leukemia, three lymphoma, and three multiple myeloma cell lines in six biological replicates. The intensities of the phosphorylation sites grouped these cancer cell lines according to their tumor type. In addition, a phosphoproteomic analysis of seven acute myeloid leukemia cell lines revealed a battery of phosphorylation sites whose combined intensities correlated with the growth-inhibitory responses to three kinase inhibitors with remarkable correlation coefficients and fold changes (> 100 between the most resistant and sensitive cells). Modeling based on regression analysis indicated that a subset of phosphorylation sites could be used to predict response to the tested drugs. Quantitative analysis of phosphorylation motifs indicated that resistant and sensitive cells differed in their patterns of kinase activities, but, interestingly, phosphorylations correlating with responses were not on members of the pathway being targeted; instead, these mainly were on parallel kinase pathways. CONCLUSION: This study reveals that the information on kinase activation encoded in phosphoproteomics data correlates remarkably well with the phenotypic responses of cancer cells to compounds that target kinase signaling and could be useful for the identification of novel markers of resistance or sensitivity to drugs that target the signaling network.

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[827]

**TÍTULO / TITLE:** - Polo-like kinase (PLK) inhibitor, Ro5203280, has potent anti-tumor activity in nasopharyngeal carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 17.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1219](#)

**AUTORES / AUTHORS:** - Kwok Leung Cheung A; Ip JC; Lung HL; Zhen Wu J; Tsao SW; Li Lung M

**INSTITUCIÓN / INSTITUTION:** - 1Clinical Oncology, The University of Hong Kong.

**RESUMEN / SUMMARY:** - Nasopharyngeal carcinoma (NPC) is a cancer with its highest prevalence among the southern Chinese and is rare elsewhere in the world. The main treatment modalities include chemotherapy and radiotherapy. However, tumor chemoresistance often limits the efficacy of NPC treatment and reduces survival rates. Thus, identifying new selective chemotherapeutic drugs for NPC treatment is needed. In this current study, the anti-tumor efficacy of a polo-like kinase inhibitor, Ro5203280, was investigated. Ro5203280 induces tumor suppression both in vitro and in vivo. An inhibitory effect was observed with the highly proliferating cancer cell lines tested, but not with the non-tumorigenic cell line. Real-time cell proliferation and FACS analysis,

together with immunohistochemical (IHC), immunofluorescence (IF), and Annexin V staining assays were used to evaluate the impact of drug treatment on cell cycle and apoptosis. Ro5203280 induces G2/M cell cycle arrest and apoptosis. Western blotting shows it inhibits PLK1 phosphorylation and down-regulates the downstream signaling molecule, Cdc25c, and up-regulates two important mitosis regulators, Wee1 and Securin, as well as the DNA damage-related factor Chk2 in vitro and in vivo. In vivo tumorigenicity assays with Ro5203280 intravenous injection demonstrated its potent ability to inhibit tumor growth in mice, with no observable signs of toxicity. These findings suggest the potential usefulness of Ro5203280 as a chemotherapeutic targeting drug for NPC treatment.

[828]

**TÍTULO / TITLE:** - Lessons learned and questions unanswered from use of multitargeted kinase inhibitors in medullary thyroid cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Oncol. 2013 Apr 9. pii: S1368-8375(13)00518-6. doi: 10.1016/j.oraloncology.2013.03.442.

●●Enlace al texto completo (gratis o de pago)

[1016/j.oraloncology.2013.03.442](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas M.D. Anderson Cancer Center, 1400 Pressler Street, Unit 1461, Houston, TX 77030, USA. Electronic address:

[sisherma@mdanderson.org](mailto:sisherma@mdanderson.org).

**RESUMEN / SUMMARY:** - OBJECTIVES: To review studies of novel multitargeted kinase inhibitors studied in patients with medullary thyroid cancer (MTC).

MATERIALS AND METHODS: Search of relevant references in PubMed and Google Scholar on “chemotherapy” and “medullary thyroid cancer”. RESULTS: Multitargeted kinase inhibitors have revolutionized the role of chemotherapy for progressive MTC, providing for the first time tolerable therapeutic options that can improve outcomes in patients with progressive disease. Drugs thought to inhibit the RET kinase have advanced the furthest for this disease, but these agents also target the VEGF receptor along with other kinases that may be relevant to both beneficial and adverse effects. Vandetanib improved progression-free survival from 19.3 to 30.5 months compared with placebo in patients with metastatic disease, whereas cabozantinib improved progression-free survival from 4.0 months to 11.2 months in a population with more aggressive disease. However, “cure” remains elusive, adverse events frequent, and exactly how such “targeted” agents actually function within MTC remains unclear. CONCLUSIONS: New approaches to clinical trial design and the preclinical development of targeted agents may be required to optimize the

combination of maximum efficacy with minimal toxicity for patients with metastatic MTC.

[829]

**TÍTULO / TITLE:** - Loss of SS18-SSX1 Inhibits Viability and Induces Apoptosis in Synovial Sarcoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Orthop Relat Res. 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s11999-013-3065-9](#)

**AUTORES / AUTHORS:** - Carmody Soni EE; Schlottman S; Erkizan HV; Uren A; Toretzky JA

**INSTITUCIÓN / INSTITUTION:** - MedStar Georgetown Orthopaedic Institute, 110 Irving Street, NW C-2173, Washington, DC, 20010, USA, [Emily.E.Soni@Medstar.net](mailto:Emily.E.Soni@Medstar.net).

**RESUMEN / SUMMARY:** - BACKGROUND: Most synovial sarcomas contain a chromosomal translocation t(X;18), which results in the formation of an oncoprotein SS18-SSX critical to the viability of synovial sarcoma. QUESTIONS/PURPOSES: We (1) established and characterized three novel synovial sarcoma cell lines and asked (2) whether inhibition of SS18-SSX1 decreases cell viability in these cell lines; and (3) whether reduction in viability after SS18-SSX1 knockdown is caused by apoptosis. After identifying a specific posttranscriptional splice variant in our cell lines, we asked (4) whether this provides a survival benefit in synovial sarcoma. METHODS: Cells lines were characterized. SS18-SSX1 knockdown was achieved using a shRNA system. Cell viability was assessed by WST-1 analysis and apoptosis examined by caspase-3 activity. RESULTS: We confirmed the SS18-SSX1 translocation in all cell lines and identified a consistent splicing variant. We achieved successful knockdown of SS18-SSX1 and with this saw a significant reduction in cell viability. Decreased viability was a result of increased apoptosis. Reintroduction of the exon 8 sequence into cells reduced cell viability in all cell lines. CONCLUSIONS: We confirmed the presence of the SS18-SSX1 translocation in our cell lines and its importance in the survival of synovial sarcoma. We have also demonstrated that reduction in cell viability is related to an increase in apoptosis. In addition, we have identified a potential mediator of SS18-SSX function in exon 8. CLINICAL RELEVANCE: SS18-SSX represents a tumor-specific target in synovial sarcoma. Exploitation of SS18-SSX and its protein partners will allow us to develop potent tumor-specific therapeutic agents.

[830]

**TÍTULO / TITLE:** - Relapse or eradication of cancer is predicted by peptide-major histocompatibility complex affinity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Cell. 2013 Apr 15;23(4):516-26. doi: 10.1016/j.ccr.2013.03.018.

●●Enlace al texto completo (gratis o de pago) [1016/j.ccr.2013.03.018](http://1016/j.ccr.2013.03.018)

**AUTORES / AUTHORS:** - Engels B; Engelhard VH; Sidney J; Sette A; Binder DC; Liu RB; Kranz DM; Meredith SC; Rowley DA; Schreiber H

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Committee on Immunology and Committee on Cancer Biology, The University of Chicago, Chicago, IL 60637, USA. [bengels@bsd.uchicago.edu](mailto:bengels@bsd.uchicago.edu)

**RESUMEN / SUMMARY:** - Cancers often relapse after adoptive therapy, even though specific T cells kill cells from the same cancer efficiently in vitro. We found that tumor eradication by T cells required high affinities of the targeted peptides for major histocompatibility complex (MHC) class I. Affinities of at least 10 nM were required for relapse-free regression. Only high-affinity peptide-MHC interactions led to efficient cross-presentation of antigen, thereby stimulating cognate T cells to secrete cytokines. These findings highlight the importance of targeting peptides with high affinity for MHC class I when designing T cell-based immunotherapy.

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[831]

**TÍTULO / TITLE:** - Antitumor effect of recombinant human interferon-beta adenovirus on esophageal squamous cell cancer in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dis Esophagus. 2013 May 3. doi: 10.1111/dote.12081.

●●Enlace al texto completo (gratis o de pago) [1111/dote.12081](http://1111/dote.12081)

**AUTORES / AUTHORS:** - Qi M; Lu D; Li Y; Qin J; Wang H; Zhang Z; Chen X; Duan F; Ma J

**INSTITUCIÓN / INSTITUTION:** - Affiliated Luoyang Central Hospital, Zhengzhou University, Luoyang.

**RESUMEN / SUMMARY:** - Interferon (IFN)-beta has efficient antitumor effect both in vitro and in vivo, but its clinical implication is limited by short half-life and systemic toxicities. Gene therapy could be the choice to avoid the defects. Adenovirus vector containing human IFN-beta gene was transfected into esophageal squamous cell carcinoma KYSE150 cells. Expression of human (h)IFN-beta was detected by reverse transcription polymerase chain reaction and immunocytochemistry in KYSE150 cells. Cell growth and clonogenic assays, and flow cytometry were used to observe the antiproliferation effect and apoptosis on tumor cells, respectively. Reverse transcription polymerase chain reaction and immunocytochemistry showed obvious hIFN-beta expression in KYSE150 cells after transfection and the tumor cell proliferation was obviously inhibited through cell proliferation and clonogenic assays. Flow cytometry

analysis showed 27.3% cell apoptosis in adenovirus vector containing human IFN-beta gene transfection group compared with 1.12% in empty vector control group. These findings indicate that hIFN-beta gene mediated by recombinant adenovirus may have antitumor activity against human esophageal carcinoma cell by inducing apoptosis in vitro.

[832]

**TÍTULO / TITLE:** - Synthesis and biological evaluation of N-(4-hydroxy-3-mercaptanaphthalen-1-yl)amides as inhibitors of angiogenesis and tumor growth.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 Apr 6;64C:377-388. doi: 10.1016/j.ejmech.2013.03.043.

●●Enlace al texto completo (gratis o de pago)

[1016/j.ejmech.2013.03.043](http://1016/j.ejmech.2013.03.043)

**AUTORES / AUTHORS:** - Xu F; Jia Y; Wen Q; Wang X; Zhang L; Zhang Y; Yang K; Xu W

**INSTITUCIÓN / INSTITUTION:** - Department of Medicinal Chemistry, School of Pharmacy, Shandong University, Ji'nan, Shandong 250012, PR China.

**RESUMEN / SUMMARY:** - A series of N-(4-hydroxy-3-mercaptanaphthalen-1-yl)amides were synthesized and investigated for their in vitro antiangiogenic activity. Among these compounds, 6d, which possesses an ortho-nitro group at the benzene ring, exhibited potent inhibitory effect on the proliferation of HUVECs, A549, K562, PC-3, HCT116, MDA-MB-231 and MCF-7 cells (IC<sub>50</sub> = 5.34, 40.53, 10.81, 52.52, 10.19, 21.37 and 2.81 μM, respectively). Meanwhile, compound 6d inhibited in vitro angiogenesis markedly in both HUVECs tube formation assay and the rat thoracic aorta rings test. Further kinase assay study showed that compound 6d had good VEGFR2, ALK, AKT1 and ABL inhibitory activities and moderate EGFR and PDGFR-beta inhibitory activities. The data supports the further investigation of this class of compounds as potential antiangiogenic and anticancer agents.

[833]

**TÍTULO / TITLE:** - Prognostic significance of pathologic complete response and Ki67 expression after neoadjuvant chemotherapy in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer. 2013 May 5.

●●Enlace al texto completo (gratis o de pago) [1007/s12282-013-0474-](http://1007/s12282-013-0474-2)

[2](#)

**AUTORES / AUTHORS:** - Yoshioka T; Hosoda M; Yamamoto M; Taguchi K; Hatanaka KC; Takakuwa E; Hatanaka Y; Matsuno Y; Yamashita H

**INSTITUCIÓN / INSTITUTION:** - Breast and Endocrine Surgery, Hokkaido University Hospital, Kita 14 Nishi 5, Kita-ku, Sapporo, 060-8648, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: Recent studies have indicated that response to chemotherapy and the prognostic impact of a pathologic complete response (pCR) after neoadjuvant chemotherapy differ among breast cancer subtypes. METHODS: Women with Stage I to III breast cancer treated with anthracycline and taxane-based neoadjuvant chemotherapy (four cycles of docetaxel every 3 weeks followed by four cycles of FEC every 3 weeks) between 2006 and 2011 were retrospectively analyzed. Trastuzumab was concurrently added to docetaxel for HER2-positive breast cancer. Expression of estrogen receptor (ER), progesterone receptor (PgR), HER2, and Ki67 was examined by immunohistochemistry in pre- and post-treatment specimens. Predictive factors for neoadjuvant chemotherapy and prognosis were analyzed by breast cancer subtype. RESULTS: Of 64 patients, 30 (47 %) were ER-positive (ER+) HER2-negative (HER2-), including eight as luminal A (Ki67 labeling index (LI) <14 %) and 22 as luminal B (Ki67 LI  $\geq$  14 %) subtypes, 11 (17 %) were ER+ HER2-positive (HER2+), 12 (19 %) were ER-negative (ER-) HER2+, and 11 (17 %) were ER- HER2-. The clinical response rates were significantly higher in luminal B, ER+ HER2+, and ER- HER2+ subtypes compared with luminal A subtype. Patients whose tumors contained high Ki67 expression effectively responded to neoadjuvant chemotherapy. Ki67 LI was a predictive marker for pCR, and all patients whose tumors achieved pCR are currently disease-free. Furthermore, high Ki67 expression in post-treatment tumors was strongly correlated with poor disease-free and overall survival regardless of subtype. CONCLUSIONS: It is necessary to establish additional strategies to improve survival for patients whose residual tumors show high Ki67 expression after neoadjuvant chemotherapy.

[834]

**TÍTULO / TITLE:** - MITOTANE LEVELS PREDICT THE OUTCOME OF PATIENTS WITH ADRENOCORTICAL CARCINOMA TREATED ADJUVANTLY FOLLOWING RADICAL RESECTION.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Endocrinol. 2013 May 23.

●●Enlace al texto completo (gratis o de pago) [1530/EJE-13-0242](#)

**AUTORES / AUTHORS:** - Terzolo M; Baudin E; Ardito A; Kroiss M; Leboulleux S; Daffara F; Perotti P; Feelders RA; Devries JH; Zaggia B; De Francia S; Volante M; Haak HR; Allolio B; Al Ghuzlan A; Fassnacht M; Berruti A

**INSTITUCIÓN / INSTITUTION:** - M Terzolo, Department of Clinical and Biological Science, Internal Medicine I, Orbassano, Italy.

**RESUMEN / SUMMARY:** - Context. Mitotane plasma concentrations  $\geq$  14 mg/l have been shown to predict tumor response and better survival in patients with advanced adrenocortical cancer (ACC). A correlation between mitotane

concentrations and patient outcome has not been demonstrated in an adjuvant setting. Objective. To compare recurrence-free survival (RFS) in patients who reached and maintained mitotane concentrations  $\geq 14$  mg/l versus patients who did not. Design and setting. Retrospective analysis at 6 referral European centers. Patients. Patients with ACC who were radically resected between 1999 and 2009 and were treated adjuvantly with mitotane targeting concentrations of 14-20 mg/l. Main outcome measures. RFS (primary) and overall survival (secondary). Results. Of the 122 patients included, 63 patients (52%) reached and maintained during a median follow-up of 36 months the target mitotane concentrations [group 1] and 59 patients (48%) did not [group 2]. ACC recurrence was observed in 22 patients of group 1 (35%) and 36 patients in group 2 (61%). In multivariate analysis, the maintenance of target mitotane concentrations was associated with a significantly prolonged RFS (HR of recurrence, 0.418, 0.22-0.79;  $P=0.007$ ) while the risk of death was not significantly altered (HR, 0.59, 0.26-1.34;  $P=0.20$ ). Grade 3-4 toxicity was observed in 11 patients (9%) and was managed with temporary mitotane discontinuation. None of the patients discontinued mitotane definitively for toxicity. Conclusions. Mitotane concentrations  $\geq 14$  mg/l predict response to adjuvant treatment being associated with a prolonged RFS. A monitored adjuvant mitotane treatment may benefit patients after radical removal of ACC.

[835]

**TÍTULO / TITLE:** - Interleukin-8 as a modulator of response to bevacizumab in preclinical models of head and neck squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Oncol. 2013 Apr 24. pii: S1368-8375(13)00536-8. doi: 10.1016/j.oraloncology.2013.03.452.

●●Enlace al texto completo (gratis o de pago)

[1016/j.oraloncology.2013.03.452](#)

**AUTORES / AUTHORS:** - Gyanchandani R; Sano D; Ortega Alves MV; Klein JD; Knapick BA; Oh S; Myers JN; Kim S

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

**RESUMEN / SUMMARY:** - OBJECTIVES: Bevacizumab, a monoclonal antibody to VEGF-A, is under active clinical evaluation in head and neck squamous cell carcinoma (HNSCC) and appears to be a promising therapy in at least a subset of patients. However, there are no reliable predictive biomarkers to identify those patients most likely to benefit. In this study, we assessed the efficacy of bevacizumab in HNSCC xenograft models to characterize escape mechanisms underlying intrinsic resistance and identify potential biomarkers of drug response. MATERIALS AND METHODS: We evaluated the angiogenic profile

of HNSCC cells from sensitive and resistant cell lines using antibody array. We further examined the role of interleukin-8 (IL-8) in contributing to resistance both in vitro and in vivo, using a loss- and gain-of-function approach. RESULTS: Angiogenic profiling indicated that resistant cells expressed higher levels of proangiogenic factors including IL-8, interleukin-1alpha (IL-1alpha), vascular endothelial growth factor (VEGF), fibroblast growth factor-a (FGF-a), and tumor necrosis factor-alpha (TNF-alpha). IL-8 was the most differentially expressed protein. IL-8 signaling compensated for VEGF inhibition in endothelial cells. Downregulation of IL-8 resulted in sensitization of resistant tumors to bevacizumab by disrupting angiogenesis and enhancing endothelial cell apoptosis. Overexpression of IL-8 in sensitive tumors conferred resistance to bevacizumab. Serum analysis of HNSCC patients treated with a bevacizumab-containing regime revealed high baseline IL-8 levels in a subset of patients refractory to treatment but not in responders. CONCLUSIONS: These results implicate IL-8 in mediating intrinsic resistance to bevacizumab in HNSCC. Hence, co-targeting of VEGF and IL-8 may help overcome resistance and enhance therapeutic efficacy.

[836]

**TÍTULO / TITLE:** - Update on bevacizumab and other angiogenesis inhibitors for brain cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Emerg Drugs. 2013 Jun;18(2):137-53. doi: 10.1517/14728214.2013.794784. Epub 2013 May 14.

●●Enlace al texto completo (gratis o de pago)

[1517/14728214.2013.794784](#)

**AUTORES / AUTHORS:** - Rinne ML; Lee EQ; Nayak L; Norden AD; Beroukhim R; Wen PY; Reardon DA

**INSTITUCIÓN / INSTITUTION:** - Dana-Farber/Brigham and Women's Cancer Center, Center for Neuro-Oncology, Boston, MA, USA.

**RESUMEN / SUMMARY:** - Introduction: Primary and metastatic brain tumors remain a major challenge. The most common primary adult malignant brain tumor, glioblastoma (GBM), confers a dismal prognosis as does the development of CNS metastases for most systemic malignancies. Anti-angiogenic therapy has been a major clinical research focus in neuro-oncology over the past 5 years. Areas covered: Culmination of this work includes US FDA accelerated approval of bevacizumab for recurrent GBM and the completion of two placebo-controlled Phase III studies of bevacizumab for newly diagnosed GBM. A multitude of anti-angiogenics are in evaluation for neuro-oncology patients but none has thus far surpassed the therapeutic benefit of bevacizumab. Expert opinion: These agents demonstrate adequate safety and the majority of GBM patients derive benefit. Furthermore, their anti-permeability effect can substantially decrease tumor-associated edema leading to stable or

improved neurologic function and quality of life. In particular, anti-angiogenics significantly prolong progression-free survival - a noteworthy achievement in the context of infiltrative and destructive brain tumors like GBM; however, in a manner analogous to other cancers, their impact on overall survival for GBM patients is modest at best. Despite substantial clinical research efforts, many fundamental questions regarding anti-angiogenic agents in brain tumor patients remain unanswered.

[837]

**TÍTULO / TITLE:** - PG545, an angiogenesis and heparanase inhibitor, reduces primary tumor growth and metastasis in experimental pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1123](#)

**AUTORES / AUTHORS:** - Ostapoff KT; Aswasthi N; Cenik BK; Hinz S; Dredge K; Schwarz RE; Brekken RA

**INSTITUCIÓN / INSTITUTION:** - 1Surgery, Division of Surgical Oncology, Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center.

**RESUMEN / SUMMARY:** - Aggressive tumor progression, metastasis and resistance to conventional therapies lead to an extremely poor prognosis for pancreatic ductal adenocarcinoma (PDAC). Heparanase, an enzyme expressed by multiple cell types including tumor cells in the tumor microenvironment, has been implicated in angiogenesis and metastasis, and its expression correlates with decreased overall survival in PDAC. We evaluated the therapeutic potential of PG545, an angiogenesis and heparanase inhibitor, in experimental PDAC. PG545 inhibited the proliferation, migration and colony formation of pancreatic cancer cells in vitro at pharmacologically relevant concentrations. Heparanase inhibition also reduced the proliferation of fibroblasts but had only modest effects on endothelial cells in vitro. Furthermore, PG545 significantly prolonged animal survival in intraperitoneal and genetic models (mPDAC: LSL-KrasG12D; Cdkn2alox/lox; p48Cre) of PDAC. PG545 also inhibited primary tumor growth and metastasis in orthotopic and genetic endpoint studies. Analysis of tumor tissue revealed that PG545 significantly decreased cell proliferation, increased apoptosis and reduced microvessel density, disrupted vascular function and elevated intratumoral hypoxia. Elevated hypoxia is a known driver of collagen deposition and tumor progression; however tumors from PG545 treated animals displayed reduced collagen deposition and a greater degree of differentiation compared to control or gemcitabine treated tumors. These results highlight the potent anti-tumor activity of PG545 and support the further exploration of heparanase inhibitors as a potential clinical strategy for the treatment of PDAC.

[838]

**TÍTULO / TITLE:** - Prostate cancer genomics by high-throughput technologies: genome-wide association study and sequencing analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Endocr Relat Cancer. 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [1530/ERC-13-0113](#)

**AUTORES / AUTHORS:** - Nakagawa H

**INSTITUCIÓN / INSTITUTION:** - H Nakagawa, Laboratory for Biomarker Development, Center for Genomic Medicine, RIKEN, Tokyo, 108-8639, Japan.

**RESUMEN / SUMMARY:** - Prostate cancer (PC) is the most common malignancy in males. It is evident that genetic factors at both germline and somatic levels play critical roles in prostate carcinogenesis. Recently, genome-wide association studies (GWAS) by high-throughput genotyping technology have identified more than 70 germline variants on various genes or chromosome loci that are significantly associated with PC susceptibility. They include multiple 8q24 loci, prostate-specific genes, and metabolism-related genes. Somatic alterations in PC genome have been explored by high-throughput sequencing technologies such as whole genome sequencing and RNA sequencing, which have identified a variety of androgen-response events and fusion transcripts represented by ETS gene fusions. Recent innovations in high-throughput genomic technologies have enabled us to analyze PC genomics more comprehensively, more precisely, and on a larger scale in multiple ethnic groups to increase our understanding of PC genomics and biology in germline and somatic studies, which can ultimately lead to personalized medicine for PC diagnosis, prevention, and therapy. However, these data indicate that the PC genome is more complex and heterogeneous than we expected from GWAS and sequencing analyses.

[839]

**TÍTULO / TITLE:** - mTOR, p70S6K, AKT and ERK1/2 levels predict sensitivity to mTOR and PI3K/mTOR inhibitors in human bronchial carcinoids.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Endocr Relat Cancer. 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1530/ERC-13-0042](#)

**AUTORES / AUTHORS:** - Gagliano T; Bellio M; Gentilin E; Mole D; Tagliati F; Schiavon M; Cavallesco NG; Andriolo LG; Rea F; Degli Uberti EC; Zatelli MC

**INSTITUCIÓN / INSTITUTION:** - T Gagliano, Department of Medical Sciences, University of Ferrara, Ferrara, Italy.

**RESUMEN / SUMMARY:** - Bronchial carcinoids (BC) are rare neuroendocrine tumors that are still orphan of medical treatment. Human BC primary cultures may display resistance to Everolimus, an inhibitor of the mammalian target of

rapamycin (mTOR), in terms of cell viability reduction. Our aim is to assess whether the novel dual PI3K/mTOR inhibitor, NVP-BEZ235, may be effective in Everolimus-resistant human BC tissues and cell lines. In addition, we search for possible markers of mTOR inhibitors efficacy, that may help in identifying the patients that may benefit from mTOR inhibitors treatment, sparing them from ineffective therapy. We found that NVP-BEZ235 is twice as potent as Everolimus in reducing cell viability and activating apoptosis in human BC tissues that display sensitivity to mTOR inhibitors, but is not effective in Everolimus-resistant BC tissues and cell lines, that by-pass cyclin D1 down-regulation and escape G0/G1 blockade. Rebound AKT activation was not observed in response to treatment with either mTOR inhibitor in 'resistant' BC cells. In addition to total mTOR levels, putative markers of BC sensitivity to mTOR inhibitors are represented by AKT, p70S6K and ERK1/2 protein levels. Finally, we validated these markers in an independent BC group. These data indicate that the dual PI3K/mTOR inhibitor NVP-BEZ235 is more potent than Everolimus in reducing human BC cell proliferation. 'Resistant' cells display lower levels of mTOR, p70S6K, AKT and ERK1/2, indicating that these proteins may be useful as predictive markers of resistance to mTOR and PI3K/mTOR inhibitors in human BC.

[840]

**TÍTULO / TITLE:** - Genetic polymorphisms of ERCC1118, XRCC1399 and GSTP1105 are associated with the clinical outcome of gastric cancer patients receiving oxaliplatinbased adjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jun;7(6):1904-11. doi: 10.3892/mmr.2013.1435. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1435](#)

**AUTORES / AUTHORS:** - Liu YP; Ling Y; Qi QF; Zhang YP; Zhang CS; Zhu CT; Wang MH; Pan YD

**INSTITUCIÓN / INSTITUTION:** - Clinical Oncology Laboratory, Changzhou Tumor Hospital Affiliated to Suzhou University, Changzhou, Jiangsu 213002, P.R. China.

**RESUMEN / SUMMARY:** - The aim of the present study was to determine whether specific molecular parameters may serve as predictors of treatment outcomes and toxicity of oxaliplatin (OXA)based chemotherapy, which is used as an adjuvant treatment in resected gastric cancer. All gastric cancer patients examined in the study received an OXA/5fluorouracil chemotherapeutic regimen. Genetic polymorphisms of certain platinumrelated genes were determined by the TaqMan 5' nuclease assay and direct sequencing. Relapsefree survival (RFS), overall survival (OS) and toxicity were evaluated according to each genotype. Following adjustment for the most relevant clinical variables, excision repair crosscomplimentary group 1 (ERCC1)118 and X-ray

repair cross-complementing protein 1 (XRCC1399) demonstrated significant predictive value for RFS and OS. We also demonstrated that carrying at least one variant XRCC1 Arg399Gln or glutathione S-transferase pi 1 (GSTP1) Ile105Val allele significantly increased the risk of any grade 3 or 4 hematological toxicity. In particular, carrying at least one variant GSTP1 Ile105Val allele was also significantly correlated with an increased risk of grade 3 or 4 gastrointestinal toxicity and neurotoxicity. Our data suggested that gastric cancer patients harboring ERCC1118 C/C and XRCC1399 A/G or A/A genotypes may benefit from receiving OXAbased adjuvant chemotherapy, and carrying at least one variant XRCC1 Arg399Gln or GSTP1 Ile105Val allele may contribute to the occurrence of adverse drug effects associated with OXAbased chemotherapy.

[841]

**TÍTULO / TITLE:** - Nuclear beta-catenin accumulation is associated with increased expression of Nanog protein and predicts poor prognosis of non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 May 6;11(1):114.

●●Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-114](#)

**AUTORES / AUTHORS:** - Li XQ; Yang XL; Zhang G; Wu SP; Deng XB; Xiao SJ; Liu QZ; Yao KT; Xiao GH

**RESUMEN / SUMMARY:** - BACKGROUND: Although the prognostic roles of beta-catenin expression in non-small cell lung cancer (NSCLC) have been reported in several immunohistochemical (IHC) studies, the results were not consistent because some studies lack sufficient number of the positive cases or did not evaluate the subcellular localization features of the protein. METHOD: In this study, we have evaluated the expression levels and subcellular localization of beta-catenin and Nanog proteins IHC staining in tissue specimens from 309 patients with NSCLC, and explored their association with clinicopathological features and patient outcome. RESULTS: We showed that patients with negative expression of membranous beta-catenin had a trend towards shorter survival ( $p=0.064$ ) than those with positive expression. In contrast to previous studies, we found that increased expression of either cytoplasmic or nuclear beta-catenin was strongly associated with poor prognosis and was an independent prognosticator for overall survival ( $p < 0.01$ ). We further found that NSCLC cells frequently exhibited an abundance of nuclear Nanog protein which was significantly correlated with nuclear beta-catenin expression ( $p < 0.01$ ) and poor prognosis ( $p < 0.01$ ). Interestingly, immunofluorescent staining results revealed that increased expression of Nanog and nuclear translocation of beta-catenin occurred concomitantly in response to epidermal growth factor receptor (EGFR) signaling in A549 and H23 cells. Furthermore, western blot analysis show that nuclear beta-catenin rather than cytoplasm beta-catenin expression in the A549 and H23 cells can be enhanced by adding EGF, Nanog

expression in the A549 and H23 cells with knockdown of beta-catenin can not be obviously enhanced by adding EGF. CONCLUSION: We propose that evaluation of subcellular localization of beta-catenin and Nanog expression is of clinical significance for patients with NSCLC.

[842]

**TÍTULO / TITLE:** - Restoring KLF5 in Esophageal Squamous Cell Cancer Cells Activates the JNK Pathway Leading to Apoptosis and Reduced Cell Survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neoplasia. 2013 May;15(5):472-80.

**AUTORES / AUTHORS:** - Tarapore RS; Yang Y; Katz JP

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Gastroenterology Division, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

**RESUMEN / SUMMARY:** - Esophageal cancer is the eighth most common cancer in the world and has an extremely dismal prognosis, with a 5-year survival of less than 20%. Current treatment options are limited, and thus identifying new molecular targets and pathways is critical to derive novel therapies. Worldwide, more than 90% of esophageal cancers are esophageal squamous cell cancer (ESCC). Previously, we identified that Kruppel-like factor 5 (KLF5), a key transcriptional regulator normally expressed in esophageal squamous epithelial cells, is lost in human ESCC. To examine the effects of restoring KLF5 in ESCC, we transduced the human ESCC cell lines TE7 and TE15, both of which lack KLF5 expression, with retrovirus to express KLF5 upon doxycycline induction. When KLF5 was induced, ESCC cells demonstrated increased apoptosis and decreased viability, with up-regulation of the proapoptotic factor BAX. Interestingly, c-Jun N-terminal kinase (JNK) signaling, an important upstream mediator of proapoptotic pathways including BAX, was also activated following KLF5 induction. KLF5 activation of JNK signaling was mediated by KLF5 transactivation of two key upstream regulators of the JNK pathway, ASK1 and MKK4, and inhibition of JNK blocked apoptosis and normalized cell survival following KLF5 induction. Thus, restoring KLF5 in ESCC cells promotes apoptosis and decreases cell survival in a JNK-dependent manner, providing a potential therapeutic target for human ESCC.

[843]

**TÍTULO / TITLE:** - DNA Repair Gene Associated with Clinical Outcome of Epithelial Ovarian Cancer Treated with Platinum-based Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):941-6.

**AUTORES / AUTHORS:** - Kang S; Sun HY; Zhou RM; Wang N; Hu P; Li Y

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynaecology, Hebei Medical University, Fourth Hospital, Shijiazhuang, China E-mail : [lykx1962@yahoo.com.cn](mailto:lykx1962@yahoo.com.cn).

**RESUMEN / SUMMARY:** - Objective: The nucleotide excision repair (NER) and base excision repair (BER) pathways, two DNA repair pathways, are related to platinum resistance in cancer treatment. In this paper, we studied the association between single nucleotide polymorphisms (SNPs) of involved genes and response to platinum-based chemotherapy in epithelial ovarian cancer. Method: Eight SNPs in XRCC1 (BER), XPC and XPD (NER) were assessed in 213 patients with epithelial ovarian cancer using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and primer-introduced restriction analysis-polymerase chain reaction (PIRA-PCR) techniques. Results: The median progression-free survival (PFS) of patients carrying the Lys/Lys and Lys/Gln+Gln/Gln genotype of the XPC Lys/Gln polymorphism were 25 and 12 months, respectively (P=0.039); and the mean overall survival (OS) of patients was 31.1 and 27.8 months, respectively (P=0.048). Cox's multivariate analysis suggested that patients with epithelial ovarian cancer with the Gln allele had an increased risk of death (HR=1.75; 95% CI=1.06-2.91) compared to those with the Lys/Lys genotype. There are no associations between the XPC PAT+/-, XRCC1 Arg194Trp, Arg280His, Arg399Gln, and XPD Asp312Asn, Lys751Gln polymorphisms and the survival of patients with epithelial ovarian cancer when treated with platinum-based chemotherapy. Conclusion: Our results indicated that the XPC Lys939Gln polymorphism may correlate with clinical outcome of patients with epithelial ovarian cancer when treated with platinum-based chemotherapy in Northern China.

[844]

**TÍTULO / TITLE:** - Prognostic and Predictive Value of Hematologic Parameters in Patients with Metastatic Renal Cell Carcinoma: Second Line Sunitinib Treatment Following IFN-alpha.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(3):2101-5.

**AUTORES / AUTHORS:** - Dirican A; Kucukzeybek Y; Erten C; Somali I; Demir L; Can A; Payzin KB; Bayoglu IV; Akyol M; Yildiz Y; Koeseoglu M; Alacacioglu A; Tarhan MO

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**RESUMEN / SUMMARY:** - Background: Long-term survival is a problem with locally advanced and metastatic renal cell carcinomas. Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor, but data on sunitinib use as a second line treatment in metastatic renal cell carcinoma (mRCC) are limited. Prognostic and predictive value of peripheral blood markers has been shown for

many cancers. Materials and Methods: Efficacy and safety profiles of sunitinib after interferon alpha were evaluated based on retrospective data for 23 patients with mRCC. Hematological parameters (neutrophils, lymphocytes, platelets, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio) were recorded at the time of metastasis. It was evaluated whether hematological parameters were prognostic and predictive factors. Results: Median progression-free survival (PFS) time was 16.5 months (95%CI: 0-34.5). Median overall survival (OS) time was 25.7 months (95%CI: 10.8-40.0). Most common side effects were neutropenia (52.2%), stomatitis (26.1%) and hand-food syndrome (26.1%). PFS was found 3.13 vs 17.1 months in patients with neutrophil / lymphocyte ratio (NLR)>3 vs NLR<=3 (p:0.012). Median OS was 6.96 vs 27.1 months in patients with NLR>3 vs NLR<=3 (p:0.001). While 75% of patients who responded to sunitinib had NLR<=3, in 72% of patients with no response to sunitinib NLR>3 was detected (p:0.036). The association between the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria and NLR was statistically significant (p:0.022). Conclusions: Data on second line sunitinib treatment following cytokine in mRCC are limited. In our study, we observed second line sunitinib treatment following IFN-alpha to be effective and tolerable. NLR appeared to have prognostic and predictive value.

[845]

**TÍTULO / TITLE:** - The Importance of Molecular Profiling in Predicting Response to Epidermal Growth Factor Receptor Family Inhibitors in Non-Small-Cell Lung Cancer: Focus on Clinical Trial Results.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lung Cancer. 2013 Apr 10. pii: S1525-7304(13)00027-2. doi: 10.1016/j.clcc.2013.01.001.

●●Enlace al texto completo (gratis o de pago) [1016/j.clcc.2013.01.001](http://1016/j.clcc.2013.01.001)

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**RESUMEN / SUMMARY:** - In recent years, the epidermal growth factor receptor (EGFR) family has become a key focus of non-small-cell lung cancer biology and targeted therapies, such as the reversible EGFR tyrosine kinase inhibitors erlotinib and gefitinib. Initially, response to these agents was associated with certain demographic and clinical characteristics; subsequently, it was discovered that these subgroups were more likely to harbor specific mutations in the EGFR gene that enhanced tumor response. However, the presence of these mutations does not equate to therapeutic success. Other aspects of EGFR family signaling, including other types of EGFR mutations, EGFR protein expression, EGFR gene amplification, mediators of downstream signaling, and other receptors with similar downstream pathways may all play a role in

response or resistance to treatment. The identification of these and other molecular determinants is driving the development of novel therapies designed to achieve improved clinical outcomes in patients.

[846]

**TÍTULO / TITLE:** - Expression of gamma-aminobutyric acid receptors on neoplastic growth and prediction of prognosis in non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 Apr 24;11:102. doi: 10.1186/1479-5876-11-102.

●●Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-102](#)

**AUTORES / AUTHORS:** - Zhang X; Zhang R; Zheng Y; Shen J; Xiao D; Li J; Shi X; Huang L; Tang H; Liu J; He J; Zhang H

**INSTITUCIÓN / INSTITUTION:** - Guangzhou Research Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, Guangdong Province, 510120, China. [hejx@vip.163.com](mailto:hejx@vip.163.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the adult mammalian brain, but exerts physiologic effects other than that on neurotransmitter in non-neuronal peripheral tissues and organs. GABA may affect cancer growth through activation GABA receptors. We investigated the gene expression of GABA receptors in tissue of non-small cell lung cancers (NSCLC) and non-cancerous tissues, and found that the gene expression of GABA receptor phenotypes was correlated with tumorigenesis and clinical prognosis. METHODS: Sixty-one snap-frozen human samples of NSCLC tissues and paired non-cancerous tissues (5cm away from tumor) were analyzed. Gene expression of GABA receptors was detected by Real-time quantitative PCR (RT-qPCR). Survival times in relation to the expression of GABA receptor phenotypes were analyzed. Human NSCLC cell lines H1299, A549, H520, H460 and human bronchial epithelial cell line BEAS-2B were used to determine the phenotypes of GABA inhibitory effects on cancer cell growth. The effects of exogenous administration of GABA on H1299 cell growth were examined. RESULTS: The gene expressions were significantly higher in NSCLC tissues than in the paired non-cancerous tissues for GABAA receptor subunit alpha3 (GABRA3, P = 0.030); for GABAA receptor subunit epsilon (GABRE, P = 0.036); and GABAB receptor subunit 2 (GABBR2, P = 0.005). Kaplan-Meier curves showed that patients with high expression of GABBR2 gene and low expression of GABRA3 gene had a better prognosis (P < 0.05). The administration of GABA resulted in suppressed proliferation of NSCLC cell lines in a dose- and time-dependent manner. The use of the GABA receptor antagonist CGP35348 could reverse the inhibitory effect. CONCLUSIONS: The pattern of GABA receptor gene phenotype expression may be involved in the regulation of tumorigenesis. A high expression of GABBR2 with a low expression of GABRA3 may predict a

better outcome. The treatment with GABA attenuates cancer cell growth in vitro. The expression of GABA receptor may be not only promising genetic therapeutic targets but may also serve as valuable prognostic markers for NSCLC.

[847]

**TÍTULO / TITLE:** - Stronger prognostic power of the CpG island methylator phenotype than methylation of individual genes in neuroblastomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Jpn J Clin Oncol. 2013 Jun;43(6):641-5. doi: 10.1093/jjco/hyt058. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1093/jjco/hyt058](http://1093/jjco/hyt058)

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**RESUMEN / SUMMARY:** - **OBJECTIVE:** The CpG island methylator phenotype is strongly associated with poor survival in neuroblastomas. Neuroblastomas with the CpG island methylator phenotype include almost all neuroblastomas with MYCN amplification, and, even among neuroblastomas without MYCN amplification, have worse prognosis. At the same time, methylation of individual tumor-suppressor genes is also reported to be associated with poor survival. The purpose of this study was to compare the prognostic power of the CpG island methylator phenotype with that of methylation of individual genes. **METHODS:** Methylation-specific polymerase chain reaction was performed for five individual genes (CASP8, EMP3, HOXA9, NR1I2 and CD44) in 140 Japanese and 152 German neuroblastomas. Kaplan-Meier analysis and log-rank tests were conducted to compare the survival between groups defined by methylation status. **RESULTS:** Among the five individual genes, only CASP8 methylation had a significant association with poor overall survival both in Japanese (hazard ratio = 3.1; 95% confidence interval = 1.5-6.4; P = 0.002) and German (hazard ratio = 4.8; 95% confidence interval = 2.1-11; P = 0.0002) neuroblastomas. HOXA9 and NR1I2 methylation were associated with poor survival only in German neuroblastomas. On the other hand, the CpG island methylator phenotype had a strong and consistent association in Japanese (hazard ratio = 22; 95% confidence interval = 5.3-93; P = 1.5 x 10<sup>(-5)</sup>) and German (hazard ratio = 9.5; 95% confidence interval = 3.2-28; P = 4.7 x 10<sup>(-5)</sup>) neuroblastomas. **CONCLUSION:** The CpG island methylator phenotype is likely to have stronger prognostic power than methylation of individual genes in neuroblastomas.

[848]

**TÍTULO / TITLE:** - Are results of targeted gene sequencing ready to be used for clinical decision making for patients with acute myelogenous leukemia?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Hematol Malig Rep. 2013 Jun;8(2):149-55. doi: 10.1007/s11899-013-0161-6.

●●Enlace al texto completo (gratis o de pago) [1007/s11899-013-0161-](#)

[6](#)

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**RESUMEN / SUMMARY:** - Acute myeloid leukemia (AML) is the most common acute leukemia in the USA, which despite recent advances, continues to have a high mortality rate. It is a biologically active disease characterized by numerous cytogenetic abnormalities and multiple genetic mutations. Next-generation sequencing (NGS) will perhaps not reveal all the factors that make AML a complex disease, but does have the potential to affect the diagnosis and risk stratification of AML patients and allow more personalized therapy. AML cells are easy to obtain from the patient and samples are only minimally contaminated with normal cells, which makes it an attractive cancer to study. Several studies have now demonstrated that the majority of AML patients are cytogenetically normal and the genome of these patients may contain fewer mutations than cancer genomes that are highly aneuploid, suggesting that mutations in diploid genomes are more likely to be pathogenetically relevant. Whole-genome, exome, transcriptome, and targeted gene sequencing studies have been conducted successfully in AML and have provided with valuable information. The challenges for the future include: reducing the cost of sequencing, understanding epigenetic changes, managing data across various platforms, separating the driver mutations from the sea of passenger mutations, and finally, educating future generations to allow a better understanding and easy availability of these complex methodologies.

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[849]

**TÍTULO / TITLE:** - Incidence and predictors of hematological side effects in chronic HCV Egyptian patients treated with PEGylated interferon and ribavirin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Indian J Gastroenterol. 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s12664-013-0336-](#)

[Z](#)

**AUTORES / AUTHORS:** - Lashin AH; Shaheen YA; Metwally MA; El-Feky HM; Hegab MF; Abbas SM

**INSTITUCIÓN / INSTITUTION:** - Hepatology, Gastroenterology, and Infectious Diseases Department, Benha University, Benha, PO Box 31518, Qualubia, Egypt.

**RESUMEN / SUMMARY:** - AIM: The aim of this paper was to study the incidence and predictors of hematological abnormalities during treatment of chronic hepatitis C virus (HCV) patients with interferon and ribavirin. METHODS: One thousand and eighty-one chronic HCV patients who were treated with PEGylated interferon alpha-2a 180 mug (n = 536) or alpha-2b 1.5 mug/kg (n = 545) plus ribavirin for 48 weeks were included. Baseline demographic, laboratory, and histopathological data and, during treatment, hematological data were collected and analyzed using univariate and multivariate analyses to identify independent predictors of hematological side effects. RESULTS: During therapy, 168 of 1,018 (15.5 %) had moderate anemia (Hb <10 and  $\geq$ 8.5 g/dL) and 88 (8.1 %) had severe anemia (Hb <8.5 g/dL). Two hundred and six patients (19.1 %) had moderate neutropenia (absolute neutrophil count (ANC) <750 and  $\geq$ 500/mm<sup>3</sup>); only 55 (5.1 %) had severe neutropenia (ANC <500/mm<sup>3</sup>). Forty-three patients (4 %) had moderate (platelet <50,000 and  $\geq$ 25,000/mm<sup>3</sup>) and 5 (1.4 %) had severe thrombocytopenia (platelet <25,000/mm<sup>3</sup>). Fibrosis stage, week 4 Hb level, and week 2 and 4 reduction level in Hb were independent predictors of moderate and severe anemia (p < 0.001). Fibrosis stage and ANC at weeks 2 and 4 were predictors of neutropenia (p < 0.001, 0.001, and 0.004, respectively). Fibrosis stage and platelet count at weeks 2 and 4 were predictors of thrombocytopenia (p < 0.001, <0.001, and 0.005, respectively). There was no association between interferon type and anemia (p = 0.57), neutropenia (p = 0.6), or thrombocytopenia (p = 0.79). CONCLUSIONS: Fibrosis stage and week 2 and 4 hematological parameter reduction levels were independent predictors of hematological side effects, which are not related to interferon type.

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[850]

**TÍTULO / TITLE:** - Protein Tyrosine Phosphatase 4A2 Expression Predicts Overall and Disease-Free Survival of Human Breast Cancer and Is Associated with Estrogen and Progesterone Receptor Status.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Horm Cancer. 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [1007/s12672-013-0141-](#)

[2](#)

**AUTORES / AUTHORS:** - Andres SA; Wittliff JL; Cheng A

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, University of Louisville-Health Sciences Center, HSC Bldg. A-512, 319 Abraham Flexner Way, Louisville, KY, 40292, USA.

**RESUMEN / SUMMARY:** - Expression of protein tyrosine phosphatase PTP4A2 (also known as PRL2) has been examined in a variety of human carcinomas,

although its role in breast cancer remains inconclusive. Since the majority of previous breast cancer studies utilized tissue biopsies composed of heterogeneous cell populations, we hypothesized that an examination of PTP4A2 expression in carcinoma cells isolated by laser capture microdissection (LCM) would provide a more accurate means of assessing its predictive value. From investigations of 247 human breast cancer biopsies collected under standardized, stringent conditions, total RNA was extracted from LCM-procured carcinoma cells to perform microarray analyses to identify gene signatures associated with breast cancer behavior. Expression of PTP4A2 was corroborated by real-time quantitative polymerase chain reaction (qPCR) and referenced to estrogen and progesterone receptor levels. Patient outcomes for overall and disease-free survival were more favorable ( $p = 0.004$  and  $p = 0.001$ , respectively) when the expression of PTP4A2 in breast carcinomas was increased compared to patients with biopsies with decreased PTP4A2 levels. PTP4A2 expression determined either by microarray or qPCR was elevated in either estrogen receptor (ER)-positive or progesterone receptor (PR)-positive breast cancer biopsies compared to ER-negative or PR-negative biopsies. However, PTP4A2 expression was only correlated with overall survival in PR-positive breast carcinomas. These data suggest that PTP4A2 mRNA expression alone may serve as a biomarker for prediction of a breast cancer patient's risk of recurrence and overall survival.

[851]

**TÍTULO / TITLE:** - The role of kinase inhibitors in the treatment of patients with acute myeloid leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am Soc Clin Oncol Educ Book. 2013;2013:313-8. doi: E10.1200/EdBook\_AM.2013.33.313.

●●Enlace al texto completo (gratis o de pago)

[1200/EdBook\\_AM.2013.33.313](#)

**AUTORES / AUTHORS:** - Smith CC; Shah NP

**INSTITUCIÓN / INSTITUTION:** - From the Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA.

**RESUMEN / SUMMARY:** - Multiple small molecule kinase inhibitors are currently undergoing development for the treatment of acute myeloid leukemia (AML). Recently, selective and potent FLT3 inhibitors such as AC220 (quizartinib) have proven clinically effective in patients with AML with FLT3 internal tandem duplication (ITD) mutations, but inhibitors of other pathologically activated kinases in AML such as c-KIT and JAK2 have achieved less clinical success. Other classes of inhibitors currently undergoing clinical development target mediators of downstream signaling pathways such as mTOR and MEK or cell cycle machinery such as aurora kinases, PLK1, or cyclin-dependent kinases.

Other than FLT3 inhibitors, most inhibitors have achieved only rare bone marrow responses, and kinase inhibitor therapy in AML remains investigational. Continuing efforts to develop kinase inhibitors for the treatment of AML will require careful selection of patients for clinical trials, translational studies to characterize responders, and investigation of combination therapy that may be capable of improving response rates and duration.

[852]

**TÍTULO / TITLE:** - Protein Expression of ZEB2 in Renal Cell Carcinoma and Its Prognostic Significance in Patient Survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 2;8(5):e62558. doi: 10.1371/journal.pone.0062558. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062558](#)

**AUTORES / AUTHORS:** - Fang Y; Wei J; Cao J; Zhao H; Liao B; Qiu S; Wang D; Luo J; Chen W

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China.

**RESUMEN / SUMMARY:** - BACKGROUND: ZEB2 has been reportedly shown to mediate the epithelial-to-mesenchymal transition (EMT) and disease aggressiveness in human tumors. However, the expression status of ZEB2 in renal cell carcinoma (RCC) and ZEB2's clinicopathologic/prognostic significance are poorly understood. METHODOLOGYPRINCIPAL FINDINGS: In this study, tissue microarray, immunohistochemistry (IHC) and western blot analyses were utilized to investigate the ZEB2 expression status in RCC and adjacent renal tissue samples. In our study, samples from 116 RCC patients treated with radical nephrectomy were used as a training set to generate a ZEB2 optimal cut-point for patient outcome by receiver operating characteristic (ROC) analysis. For validation, the correlation of ZEB2 expression with the clinical characteristics and patient outcomes in another set (including 113 patients) was analyzed to validate the obtained cut-point. In the training and validation sets, high expression of ZEB2, defined by ROC analysis, predicted a poorer overall survival and progression-free survival, as evidenced by the univariate and multivariate analyses. In different subsets of overall patients, ZEB2 expression was also a prognostic indicator in patients with stage I/II, stage III/IV, grade 1/2 and grade 3/4 disease (P<0.05). Downregulation of ZEB2 by shRNA decreased the migration and invasion ability of 769-P cells in vitro. Furthermore, high ZEB2 expression was positively correlated with vimentin expression and inversely linked to E-cadherin expression in RCC. CONCLUSIONSSIGNIFICANCE: Our findings provide a basis for the concept that high ZEB2 expression in RCC may be important in the acquisition of an aggressive phenotype. This evidence suggests that ZEB2 overexpression

(examined by IHC) is an independent biomarker for the poor prognosis of patients with RCC.

[853]

**TÍTULO / TITLE:** - Reduced relative dose intensity of primary chemotherapy does not influence prognosis of patients with Hodgkin lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013 Apr 10. doi: 10.5507/bp.2013.022.

●●Enlace al texto completo (gratis o de pago) [5507/bp.2013.022](#)

**AUTORES / AUTHORS:** - Raida L; Papajik T; Rusinakova Z; Prochazka V; Faber E; Cahova D; Tucek P; Indrak K

**INSTITUCIÓN / INSTITUTION:** - Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic.

**RESUMEN / SUMMARY:** - AIMS: A retrospective analysis of patients with Hodgkin lymphoma (HL) was performed to assess their outcome regarding relative dose intensity (RDI) of chemotherapy administered in primary treatment. METHODS: A total of 194 patients were divided into three groups with different RDI of primary chemotherapy (100%, 90-99% and < 90%). Reduced RDI in two groups (90-99% and < 90%) was caused by the delay of the interval between the administration of some chemotherapeutic courses. The probability of complete remission (CR), disease relapse, event-free survival (EFS) and overall survival (OS) as the basic parameters of patient outcome were statistically compared. RESULTS: Multivariate analysis showed here were no significant differences in probability of CR (HR 0.9, 95% CI [0.75-1.08], P=0.5), risk of relapse (HR 1.34, 95% CI [0.92-1.94], P=0.11) or death (HR 1.52, 95% CI [0.94-2.5], P=0.13). There were also no significant differences in probability of EFS (mean 13 vs. 10 vs. 12 years, P=0.17; HR 1.54, 95% CI [0.91-2.6], P=0.22) or OS (mean 15 vs. 13 vs. 14 years, P=0.13; HR 1.52, 95% CI [0.93-2.5], P=0.13). CONCLUSION: We found no significant impact of primary chemotherapy delay resulting in reduced RDI on outcome in HL patients.

[854]

**TÍTULO / TITLE:** - Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer. 2013 Apr 13.

●●Enlace al texto completo (gratis o de pago) [1007/s12282-013-0464-](#)

[4](#)

**AUTORES / AUTHORS:** - Ono M; Tsuda H; Yunokawa M; Yonemori K; Shimizu C; Tamura K; Kinoshita T; Fujiwara Y

**INSTITUCIÓN / INSTITUTION:** - Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo, Japan, [makono@ncc.go.jp](mailto:makono@ncc.go.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The criteria for classifying hormone receptor (HR)-positive/HER2-negative breast cancers into low-risk and high-risk subgroups remain undetermined. Supportive data for optimal criteria to identify tumors in the high-risk subgroup are necessary for Japanese patients with HR-positive/HER2-negative breast cancers. METHODS: Using immunohistochemistry and fluorescence in situ hybridization, we identified 369 consecutive patients with HR-positive/HER2-negative, node-negative invasive breast cancers. We examined the prognostic impact of the Ki-67 labeling index (LI) based on 3 cutoff values, 10, 14, and 20 %, along with that of histological grade (HG) and nuclear grade (NG) by Cox's univariate and multivariate analyses. RESULTS: The univariate analyses clearly showed that Ki-67 LI with any cutoff value divided the patients into distinct high-risk and low-risk groups, and that HG and NG were also powerful prognostic indicators. High Ki-67 LI with any cutoff value was strongly correlated with HG and NG, and when these parameters were included in the multivariate analyses, the impact of HG/NG was stronger than Ki-67 LIs. When the 10 % cutoff value was adopted, discordance between Ki-67 LI and grades was frequent in papillotubular-type invasive ductal carcinoma, predominantly intraductal carcinoma, and mucinous carcinoma. CONCLUSIONS: Any of the Ki-67 LI values, regardless of cutoff value, could be applicable for the classification of high-risk and low-risk HR-positive/HER2-negative, node-negative invasive breast cancers. Luminal A/B subtyping according to Ki-67 LI, or HG/NG, in combination with histological type, appeared to be able to create an optimum risk estimation system for patients with HR-positive/HER2-negative, node-negative invasive breast cancers in Japan.

[855]

**TÍTULO / TITLE:** - Circulating tumor cells in HER2-positive metastatic breast cancer patients: a valuable prognostic and predictive biomarker.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Apr 23;13:202. doi: 10.1186/1471-2407-13-202.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-202](https://doi.org/10.1186/1471-2407-13-202)

**AUTORES / AUTHORS:** - Liu Y; Liu Q; Wang T; Bian L; Zhang S; Hu H; Li S; Hu Z; Wu S; Liu B; Jiang Z

**INSTITUCIÓN / INSTITUTION:** - Department of Breast Cancer, Affiliated Hospital of Academy of Military Medical Sciences, No,8 Dongdajie, Beijing, 100071, China. [bingliu17@yahoo.com](mailto:bingliu17@yahoo.com).

**RESUMEN / SUMMARY:** - BACKGROUND: This study was initiated to investigate the prognostic significance of circulating tumor cell (CTC) enumeration and the predictive value of CTC HER2 expression for efficient anti-HER2 therapy in

HER2-positive metastatic breast cancer (MBC) patients. METHODS: Sixty HER2-positive MBC patients were enrolled in the present study. Before the initiation of systemic treatment, CTCs from 7.5 ml of blood were analyzed using the CellSearch system. The progression-free survival (PFS) of the patients was estimated using Kaplan-Meier survival curves. RESULTS: CTCs were detected in 45% (27/60) of the patients, who had shorter median PFS than those without CTCs (2.5 vs. 7.5 months, P = 0.0125). Furthermore, referring to the standard HER2 testing that uses immunohistochemistry (IHC), we proposed a CTC HER2-positive criterion, defined as >30% of CTCs over-expressing HER2. Among patients undergoing anti-HER2 therapy, those with HER2-positive CTCs had longer PFS (8.8 vs. 2.5 months, P = 0.002). Among patients with HER2-positive CTCs, the median PFS for those receiving anti-HER2 therapy was significantly longer than those who were not (8.8 vs. 1.5 months, P = 0.001). Notably, up to 52% (14/27) of the HER2-positive patients were CTC HER2-negative, and anti-HER2 therapy did not significantly improve the median PFS in these patients (2.5 vs. 0.9 months, P = 0.499). CONCLUSIONS: Our findings underscore the necessity of a comprehensive CTC analysis, which may provide valuable prognostic and predictive information for optimizing individually tailored therapies in HER2-positive MBC patients. To test this idea, additional large cohort, multi-center and prospective clinical trials are needed.

[856]

**TÍTULO / TITLE:** - Predictive Value of Pretreatment BCR-ABL(IS) Transcript level on Response to Imatinib Therapy in Egyptian Patients with Chronic Phase Chronic Myeloid Leukemia (CPCML).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biomed Sci. 2013 Mar;9(1):48-53.

**AUTORES / AUTHORS:** - El-Metnawy WH; Mattar MM; El-Nahass YH; Samra MA; Abdelhamid HM; Abdelfattah RM; Hamed AR

**INSTITUCIÓN / INSTITUTION:** - Clinical Oncology Center, School of Medicine, Cairo University, Egypt;

**RESUMEN / SUMMARY:** - BACKGROUND: A wide range of responses of patients with CPCML to IM has been reported. Several factors were proposed to predict response including molecular response at 3 and 6 months. PURPOSE: To study the impact of pretreatment BCR-ABL transcript level on molecular response to IM, and to assess the value of the milestone ;  $\leq 10\%$  transcript at 3 months on PFS and OS. PATIENTS AND METHODS: Fifty five adult CP-CML patients receiving daily dose of 400 mg IM were subjected to molecular and cytogenetic analysis at diagnosis and at regular time intervals. Median follow up period was 36 months (15-48). Hematologic, cytogenetic, and molecular responses were rated according to ELN. RESULTS: Two Patient groups were distinguished regarding response to IM therapy. A group of 22/55 patients (40%) having pretreatment BCR-ABL(IS) level  $\leq 200\%$  and a second patient group 33/55 (60%) having transcript level  $> 200\%$ . The  $\leq 10\%$  milestone was

achieved by 15/22 patients (68%) versus 7/33 patients (21%),  $p=0.04$  in favor of the first group. Optimal responders in first group were 14/22 (64%) compared to 13/33 (39%) in second group,  $p=0.02$ . Achievement of 10% transcript level significantly correlated with longer PFS. The median BCR-ABL(IS) transcripts levels in optimal responders at 3, 6 and 18 months was 10%, 2% and 0.1%, respectively compared to 100%, 65% and 10%, in suboptimal/resistant patients  $p=0.001$ . Resistance in 11 patients was correlated with identifiable ABL Kinase mutations. CONCLUSIONS: The Pretreatment 200% cutoff and the 3 month BCR-ABL(IS)  $\leq 10\%$  transcript levels proved strong predictors of response to IM and significantly correlated with probability of CCyR, MMR and PFS.

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[857]

**TÍTULO / TITLE:** - Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J BUON. 2013 Jan-Mar;18(1):188-94.

**AUTORES / AUTHORS:** - Grigorescu AC; Bala C

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, "Prof. Dr. Alexandru Trestioreanu" Oncology Institute, Bucharest, Romania.

**RESUMEN / SUMMARY:** - Purpose: The purpose of the present trial was to investigate whether clinical benefit can be obtained by concurrent administration of erlotinib with gemcitabine as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) and ECOG performance status (PS) 2. Methods: Included were chemotherapy-naive patients with histologically/cytologically documented unresectable advanced and/or metastatic (stage IIIB/IV) NSCLC and ECOG PS 2. In this phase II, single-arm study, all patients received first-line gemcitabine plus erlotinib for 6 cycles or until disease progression, unacceptable toxicity or patient withdrawal due to any reason. The primary study objectives were the evaluation of disease response and the time to progression. Secondary objectives included evaluation of overall survival and the safety profile of gemcitabine plus erlotinib. Results: Nineteen eligible patients were studied. The overall response rate (complete response/CR and partial response/PR) was 15.8% and the clinical benefit rate (CR+PR+stable disease/SD) 36.84%. The median overall survival for the whole study group was 39 weeks (95% CI 27-51) and the median time to disease progression for 19 evaluable patients was 15 weeks (95% CI 7-36). The safety profile of the combination was acceptable with only 2 serious adverse events. Conclusion: Taking into account similar published clinical studies we conclude that gemcitabine plus erlotinib achieve superior response rate and comparable overall survival with acceptable toxicity compared to monochemotherapy with gemcitabine. This combination represents a treatment option for patients with advanced NSCLC and ECOG PS 2.

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[858]

**TÍTULO / TITLE:** - XPG is Predictive Gene of Clinical Outcome in Advanced Non-small-cell Lung Cancer with Platinum Drug Therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):701-5.

**AUTORES / AUTHORS:** - Zhang T; Sun J; Lv M; Zhang L; Wang X; Ren JC; Wang B

**INSTITUCIÓN / INSTITUTION:** - Department of Radiotherapy, Beijing Chaoyang Hospital, Capital Medical University, Changchun, China E-mail : [wangxia\\_xxmc@163.com](mailto:wangxia_xxmc@163.com).

**RESUMEN / SUMMARY:** - Polymorphisms in XPG are considered to contribute to the clinical outcome of patients receiving platinum drug chemotherapy. We aimed to investigate the role of five potential SNPs of XPG gene on the response to platinum-based chemotherapy in advanced Chinese NSCLC patients. A total of 451 patients with newly diagnosed and histopathologically confirmed primary NSCLC were consecutively collected. XPG rs2296147, rs4150261, rs17655, rs1047768 and rs2094258 were genotyped by the Taqman real-time polymerase chain reaction (PCR). In our study, we found patients carrying rs1057768 TT genotype had a significantly lower treatment response when compared with the CC genotype (OR=0.38, 95% CI=0.18-0.78). Patients carrying rs1047768 TT genotype showed a significantly short median PFS (11.2 months) and OS (13.6 months) than CC genotype, and the hazard ratios (HR) for PFS and OS were 2.06 (1.01-4.50) and 2.29 (1.21-2.49), respectively. Moreover, we found a significant decreased risk of death from NSCLC among patients carrying the rs2296147 TT genotype when compared with the CC genotype, the HR (95% CI) for OS being 0.50 (0.27-0.95). In conclusion, our study found that polymorphisms in rs1047768 C/T and rs2296147 C/T are associated with response to platinum-based chemotherapy in advanced NSCLC, and XPG polymorphisms could be predictive of prognosis.

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[859]

**TÍTULO / TITLE:** - Quantification of Her-2/Neu Gene in Breast Cancer Patients using Real Time-Polymerase Chain Reaction (Q-PCR) and Correlation with Immunohistochemistry Findings.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(3):1655-9.

**AUTORES / AUTHORS:** - Abdul Murad NA; Razak ZA; Hussain RM; Syed Hussain SN; Ko Ching Huat C; Che Md Ali SA; Abdullah N; Muhammad R; Ibrahim N; Jamal R

**INSTITUCIÓN / INSTITUTION:** - UKM Medical Molecular Biology Institute, Kuala Lumpur, Malaysia E-mail : [rahmanj@ppukm.ukm.edu.my](mailto:rahmanj@ppukm.ukm.edu.my).

**RESUMEN / SUMMARY:** - Background: HER-2/neu is a proto-oncogene that encodes a transmembrane tyrosine kinase growth factor which is crucial for stimulating growth and cellular motility. Overexpression of HER-2/neu is

observed in 10-35% of human breast cancers and is associated with pathogenesis, prognosis as well as response to therapy. Given the imperative role of HER-2/neu overexpression in breast cancer, it is important to determine the magnitude of amplification which may facilitate a better prognosis as well as personalized therapy in affected patients. In this study, we determined HER-2/neu protein expression by immunohistochemistry (IHC) concurrently with HER-2/neu DNA amplification by quantitative real time-polymerase chain reaction (Q-PCR). Materials and Methods: A total of 53 paired tissue samples from breast cancer patients were frozen-sectioned to characterize the tumour and normal tissues. Only tissues with 80% tumour cells were used in this study. For confirmation, Q-PCR was used to determine the HER-2/neu DNA amplification. Results: We found 20/53 (37.7%) of the tumour tissues to be positive for HER-2/neu protein overexpression using IHC. Out of these twenty, only 9/53 (17%) cases were in agreement with the Q-PCR results. The concordance rate between IHC and Q-PCR was 79.3%. Approximately 20.7% of positive IHC cases showed no HER-2/neu gene amplification using Q-PCR. Conclusion: In conclusion, IHC can be used as an initial screening method for detection of the HER-2/neu protein overexpression. Techniques such as Q-PCR should be employed to verify the IHC results for uncertain cases as well as determination of HER-2/neu gene amplification.

[860]

**TÍTULO / TITLE:** - Prognostic significance of syndecan-1 expression in squamous cell carcinoma of the tonsil.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Oncol. 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1007/s10147-013-0552-](#)

[7](#)

**AUTORES / AUTHORS:** - Lee SH; Choi EJ; Kim MS; Park JW; Lee YS; Kim SY; Kang CS

**INSTITUCIÓN / INSTITUTION:** - Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Banpodaero 222 Socho-gu, Seoul, 137-701, Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Syndecan-1 (SDC1) is reported to modulate several key processes of tumorigenesis and to show variable expression in many cancers. The cause of these variations in expression is not known to date. In this study, we compared SDC1 status with clinicopathologic parameters to evaluate the prognostic implications of SDC1 status on squamous cell carcinoma (SCC) of the tonsil. METHODS: In 56 cases of tonsillar SCC, we screened SDC1 expression using immunohistochemistry and analyzed the relationships between SDC1 expression and clinicopathological parameters. To identify the cause of the changes in SDC1 expression seen in tumors, we measured the gene dosage of SDC1 in tumor cells using fluorescent

in situ hybridization. RESULTS: SDC1 expression was found in cancer cells in 36 cases (64.3 %) of tonsillar SCC. It was associated with lymph node metastasis ( $p = 0.010$ ) and a positive surgical resection margin ( $p = 0.014$ ). On the other hand, it was not significantly correlated with sex, age, smoking status, degree of differentiation, T stage, or distant metastasis. We could not find any copy-number variation of SDC1 in the cases showing increased SDC1 immunopositivity. In addition, strong SDC1 expression in the tumor cells predicted a shorter overall survival ( $p = 0.020$ , log-rank). CONCLUSIONS: We showed that SDC1 expression is associated with N stage and the status of resection margin involvement in SCC of the tonsil. With respect to survival, there were unfavorable outcomes in cases with SDC1 positivity. More studies are needed to better understand the role of SDC1 in the progression and invasiveness of tonsillar SCC.

[861]

**TÍTULO / TITLE:** - The role of globular heads of the C1q receptor in HPV 16 E2-induced human cervical squamous carcinoma cell apoptosis is associated with p38 MAPK/JNK activation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 May 8;11:118. doi: 10.1186/1479-5876-11-118.

●●Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-118](#)

**AUTORES / AUTHORS:** - Gao LJ; Gu PQ; Zhao W; Ding WY; Zhao XQ; Guo SY; Zhong TY

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Reproductive Medicine, Department of Clinical Laboratory, Nanjing Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University, Tianfei Alley, Nanjing Mochou Road, Nanjing, 210004, P,R, China. [gaolingjuan@njmu.edu.cn](mailto:gaolingjuan@njmu.edu.cn).

**RESUMEN / SUMMARY:** - BACKGROUND: Human papillomavirus type 16 (HPV 16) E2 protein is a multifunctional DNA-binding protein. HPV 16 E2 regulates many biological responses, including DNA replication, gene expression, and apoptosis. The purpose of this study was to investigate the relationship among the receptor for globular heads of the human C1q (gC1qR) gene expression, HPV 16 E2 transfection and apoptosis regulation in human cervical squamous carcinoma cells (C33a and SiHa). METHODS: gC1qR expression was examined in C33a and SiHa cells using real-time PCR and Western blot analysis. Apoptosis of C33a and SiHa cells was assessed by flow cytometry. C33a and SiHa cell viability, migration and proliferation were detected using the water-soluble tetrazolium salt (WST-1) assay, a transwell assay and 3H-thymidine incorporation into DNA (3H-TdR), respectively. RESULTS: C33a and SiHa cells that were transfected with a vector encoding HPV 16 E2 displayed significantly increased gC1qR gene expression and p38 mitogen-activated protein kinase (p38 MAPK)/ c-jun N-terminal kinase (JNK) activation as well as

up-regulation of cellular apoptosis, which was abrogated by the addition of gC1qR small interfering RNA (siRNA). Furthermore, the changes in C33a and SiHa cell viability, migration and proliferation that were observed upon HPV 16 E2 transfection were abrogated by SB203580 (a p38 MAPK inhibitor) or SP600125 (a JNK inhibitor) treatment. CONCLUSION: These data support a mechanism whereby HPV 16 E2 induces apoptosis by silencing the gC1qR gene or inhibiting p38 MAPK/JNK signalling in cervical squamous cell carcinoma.

[862]

**TÍTULO / TITLE:** - The Association between COX-2 Polymorphisms and Hematologic Toxicity in Patients with Advanced Non-Small-Cell Lung Cancer Treated with Platinum-Based Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 19;8(4):e61585. doi: 10.1371/journal.pone.0061585. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061585](http://dx.doi.org/10.1371/journal.pone.0061585)

**AUTORES / AUTHORS:** - Zhou F; Gao G; Ren S; Li X; He Y; Zhou C

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Tongji University Cancer Institute, Shanghai, China.

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVE: Overexpression of COX-2 is proved to contribute to tumor promotion and carcinogenesis through stimulating cell proliferation, inhibiting apoptosis and enhancing the invasiveness of cancer cells. Apoptosis-related molecules are potential predictive markers for survival and toxicity in platinum treatment. This study aimed at investigating the association between COX-2 polymorphisms and the occurrence of grade 3 or 4 toxicity in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. MATERIALS AND METHODS: Two hundred and twelve patients with inoperable stage IIIB-IV NSCLC received first-line chemotherapy between 2007 and 2009 were recruited in this study. Four functional COX-2 polymorphisms were genotyped by PCR-based restriction fragment length polymorphism (RFLP) methods. RESULTS: The incidence of grade 3 or 4 hematologic toxicity was significantly higher in G allele carriers of the COX-2 rs689466 (-1195G/A) polymorphism compared with wild-type homozygotes AA (P value = 0.008; odds ratio, 2.47; 95% confidence interval, 1.26-4.84) and the significance still existed after the Bonferroni correction. Statistically significant difference was also found in grade 3 or 4 leukopenia (P value = 0.010; OR = 2.82; 95%CI = 1.28-6.20). No other significant association was observed between genotype and toxicity in the study. The haplotype analysis showed that the haplotype AGG was associated with a reduced risk of grade 3 or 4 hematologic and leukopenia toxicity (P value

= 0.009; OR = 0.59; 95%CI = 0.39-0.88 and P value = 0.025; OR = 0.61; 95%CI = 0.39-0.94, respectively) while the haplotype GGG was associated with an increased risk of grade 3 or 4 hematologic and leukopenia toxicity (P value = 0.009; OR = 1.71; 95%CI = 1.14-2.56 and P value = 0.025; OR = 1.65; 95%CI = 1.06-2.57, respectively). CONCLUSION: This investigation for the first time suggested that polymorphism in COX-2 rs689466 may be a potent bio-marker in predicting severe hematologic toxicity in NSCLC patients after platinum-based chemotherapy.

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[863]

**TÍTULO / TITLE:** - Pharmacogenomic assessment of outcomes of pemetrexed-treated patients with adenocarcinoma of the lung.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Yonsei Med J. 2013 Jul 1;54(4):854-64. doi: 10.3349/ymj.2013.54.4.854.

●●Enlace al texto completo (gratis o de pago) [3349/ymj.2013.54.4.854](#)

**AUTORES / AUTHORS:** - Jung M; Lee CH; Park HS; Lee JH; Kang YA; Kim SK; Chang J; Kim DJ; Rha SY; Kim JH; Cho BC

**INSTITUCIÓN / INSTITUTION:** - Yonsei Cancer Center, Division of Medical Oncology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea. [cbc1971@yuhs.ac](mailto:cbc1971@yuhs.ac).

**RESUMEN / SUMMARY:** - Purpose: The main objective of this study was to evaluate the association between polymorphisms of the target genes of pemetrexed and clinical outcomes in non-small cell lung cancer (NSCLC) patients treated with pemetrexed. Materials and Methods: We assessed polymorphisms at 8 sites in 4 genes [thymidylate synthase (TS), dihydrofolate reductase (DHFR; 1610, 680, 317, intron 1), methylenetetrahydrofolate reductase (MTHFR; 677, 1298), glycinamide ribonucleotide formyl transferase (GARFT; 2255)] associated with pemetrexed metabolism using polymerase chain reaction, gene scanning, and restriction fragment length polymorphism analysis in 90 patients with adenocarcinoma of the lung. Results: Survival was significantly longer with pemetrexed in patients with TS 3RGCC/3RGCC or 3RGGC/3RGGC compared with the other groups (PFS; 5.2 months vs. 3.7 months, p=0.03; OS; 31.8 months vs. 18.5 months, p=0.001). Patients with DHFR 680CC experienced fatigue more frequently (50% vs. 8.6%, p=0.008). Polymorphisms of MTHFR and GARFT were not significantly associated with clinical outcomes of pemetrexed. Conclusion: The TS genotype was associated with survival and one DHFR polymorphism was associated with fatigue in NSCLC patients treated with pemetrexed. Further large prospective studies are required to identify other biomarkers that affect patients being treated with pemetrexed for adenocarcinoma of the lung.

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[864]

**TÍTULO / TITLE:** - RANK/RANK-L/OPG in Patients with Bone Metastases Treated with Anticancer Agents and Zoledronic Acid: A Prospective Study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Sci. 2013 May 23;14(6):10683-93. doi: 10.3390/ijms140610683.

●●Enlace al texto completo (gratis o de pago) [3390/ijms140610683](#)

**AUTORES / AUTHORS:** - Mercatali L; Ricci M; Scarpi E; Serra P; Fabbri F; Ricci R; Liverani C; Zanoni M; Zoli W; Maltoni R; Gunelli E; Amadori D; Ibrahim T

**INSTITUCIÓN / INSTITUTION:** - Osteoncology and Rare Tumors Center, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), via P. Maroncelli 40, 47014 Meldola (FC), Italy. [t.ibrahim@irst.emr.it](mailto:t.ibrahim@irst.emr.it).

**RESUMEN / SUMMARY:** - Patients with solid cancer frequently develop bone metastases (BM). Zoledronic acid (Zometa®, ZA), routinely used to treat patients with BM, acts on osteoclasts and also has antitumor properties. We aimed to assess the effect of ZA over time in novel bone turnover markers (RANK/receptor activator of nuclear factor- $\kappa$ B ligand (RANK-L)/Osteoprotegerin (OPG)) and to correlate these with serum N-terminal telopeptide (NTX). The study prospectively evaluated levels of RANK, RANK-L and OPG transcripts by real-time PCR and NTX expression by ELISA in the peripheral blood of 49 consecutive patients with advanced breast, lung or prostate cancer. All patients received the standard ZA schedule and were monitored for 12 months. Median baseline values of RANK, RANK-L and OPG were 78.28 (range 7.34-620.64), 319.06 (21.42-1884.41) and 1.52 (0.10-58.02), respectively. At 12 months, the median RANK-L value had decreased by 22% with respect to the baseline, whereas median OPG levels had increased by about 96%. Consequently, the RANK-L/OPG ratio decreased by 56% from the baseline. Median serum NTX levels decreased over the 12-month period, reaching statistical significance ( $p < 0.0001$ ). Our results would seem to indicate that ZA modulates RANK, RANK-L and OPG expression, thus decreasing osteoclast activity.

[865]

**TÍTULO / TITLE:** - A patient tumor transplant model of squamous cell cancer identifies PI3K inhibitors as candidate therapeutics in defined molecular bins.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Oncol. 2013 Apr 4. pii: S1574-7891(13)00060-4. doi: 10.1016/j.molonc.2013.03.004.

●●Enlace al texto completo (gratis o de pago)

[1016/j.molonc.2013.03.004](#)

**AUTORES / AUTHORS:** - Keysar SB; Astling DP; Anderson RT; Vogler BW; Bowles DW; Morton JJ; Paylor JJ; Glogowska MJ; Le PN; Eagles-Soukup JR; Kako SL; Takimoto SM; Sehrt DB; Umpierrez A; Pittman MA; Macfadden SM; Helber RM; Peterson S; Hausman DF; Said S; Leem TH; Goddard JA; Arcaroli

JJ; Messersmith WA; Robinson WA; Hirsch FR; Varella-Garcia M; Raben D; Wang XJ; Song JI; Tan AC; Jimeno A

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, Department of Medicine, University of Colorado School of Medicine (UCSOM), Aurora, CO 80045, United States.

**RESUMEN / SUMMARY:** - Targeted therapy development in head and neck squamous cell carcinoma (HNSCC) is challenging given the rarity of activating mutations. Additionally, HNSCC incidence is increasing related to human papillomavirus (HPV). We sought to develop an in vivo model derived from patients reflecting the evolving HNSCC epidemiologic landscape, and use it to identify new therapies. Primary and relapsed tumors from HNSCC patients, both HPV+ and HPV-, were implanted on mice, giving rise to 25 strains. Resulting xenografts were characterized by detecting key mutations, measuring protein expression by IHC and gene expression/pathway analysis by mRNA-sequencing. Drug efficacy studies were run with representative xenografts using the approved drug cetuximab as well as the new PI3K inhibitor PX-866. Tumors maintained their original morphology, genetic profiles and drug susceptibilities through serial passaging. The genetic makeup of these tumors was consistent with known frequencies of TP53, PI3KCA, NOTCH1 and NOTCH2 mutations. Because the EGFR inhibitor cetuximab is a standard HNSCC therapy, we tested its efficacy and observed a wide spectrum of efficacy. Cetuximab-resistant strains had higher PI3K/Akt pathway gene expression and protein activation than cetuximab-sensitive strains. The PI3K inhibitor PX-866 had anti-tumor efficacy in HNSCC models with PIK3CA alterations. Finally, PI3K inhibition was effective in two cases with NOTCH1 inactivating mutations. In summary, we have developed an HNSCC model covering its clinical spectrum whose major genetic alterations and susceptibility to anticancer agents represent contemporary HNSCC. This model enables to prospectively test therapeutic-oriented hypotheses leading to personalized medicine.

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[866]

**TÍTULO / TITLE:** - Use of archived biopsy specimens to study gene expression in oral mucosa from chemotherapy-treated cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 May;115(5):630-7. doi: 10.1016/j.oooo.2013.01.003. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago) [1016/j.oooo.2013.01.003](#)

**AUTORES / AUTHORS:** - Mougeot JL; Mougeot FK; Peterson DE; Padilla RJ; Brennan MT; Lockhart PB

**INSTITUCIÓN / INSTITUTION:** - Cannon Research Center, Carolinas Medical Center, Charlotte, NC 28203, USA.

**RESUMEN / SUMMARY:** - OBJECTIVES: Oral mucositis caused by cancer chemotherapy can result in significant clinical complications. There is a strategic need to accelerate the delineation of the pathobiology. This proof-of-principle

study was designed to demonstrate the feasibility of studying archived oral mucosal specimens to further delineate oral mucositis pathobiology. MATERIALS AND METHODS: Twenty-nine formalin-fixed and paraffin-embedded tissue blocks of 25-year-old oral mucosa autopsy specimens from cancer chemotherapy patients were studied. Standardized technology was utilized, including RNA isolation and amplification, array hybridization, and gene expression analysis. RESULTS: A predominance of DNA damage in buccal mucosal basal keratinocytes was observed. Data comparing basal cells from buccal vs. gingival mucosa identified differential gene expression of host responses in relation to pathways relevant to oral mucositis pathogenesis, including responses to cancer-associated inflammation. CONCLUSIONS: This proof-of-principle study demonstrated that archived oral mucosal specimens may be a potentially valuable resource for the study of oral mucositis in cancer patients.

[867]

**TÍTULO / TITLE:** - Editorial Comment from Dr Chen to Reduction of prostate cancer incidence by naftopidil, an alpha1-adrenoceptor antagonist and transforming growth factor-beta signaling inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Urol. 2013 Apr 21. doi: 10.1111/iju.12174.

●●Enlace al texto completo (gratis o de pago) [1111/iju.12174](#)

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[868]

**TÍTULO / TITLE:** - Reduction of prostate cancer incidence by naftopidil, an alpha - adrenoceptor antagonist and transforming growth factor-beta signaling inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Urol. 2013 Apr 21. doi: 10.1111/iju.12156.

●●Enlace al texto completo (gratis o de pago) [1111/iju.12156](#)

**AUTORES / AUTHORS:** - Yamada D; Nishimatsu H; Kumano S; Hirano Y; Suzuki M; Fujimura T; Fukuhara H; Enomoto Y; Kume H; Homma Y

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, The University of Tokyo Hospital; Department of Urology, The Fraternity Memorial Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** - OBJECTIVES: Quinazoline-based alpha1 - adrenoceptor antagonists are known to inhibit prostate tumor growth through induction of apoptosis. We investigated the effect of a naphthalene-based alpha1 -adrenoceptor antagonist, naftopidil, on prostate cancer incidence, apoptosis of prostatic cell and transforming growth factor-beta signaling. METHODS: Prescription records were linked to pathological data for men who

continued naftopidil (n = 766) or tamsulosin (n = 1015) for 3 months or longer between 2003 and 2010. Prostate cancer incidence was analyzed by log-rank test and the Cox proportional hazards model. Apoptosis and cell cycle arrest in human tissues were assessed by immunohistochemical detection of Bcl2 and p21, respectively. Growth inhibition and apoptosis treatment with naftopidil and tamsulosin were assessed in cancer cell lines. Interference with transforming growth factor-beta signaling was examined by western blot analysis. RESULTS: Prostate cancer incidence was significantly lower in men who received naftopidil for 3 months or longer compared with tamsulosin (P = 0.035). Multivariate analysis confirmed a decreased hazard ratio, 0.46, for naftopidil use (P = 0.013), which was more evident with longer treatment. Immunohistochemical positivity for Bcl2, a marker for resistance to apoptosis, was less frequently detected in prostate cancer cells of men who received naftopidil compared with tamsulosin (P < 0.05). Naftopidil inhibited cancer cell growth, induced apoptosis and blocked Smad2 phosphorylation activated by transforming growth factor-beta in cell lines, with a half maximal inhibitory concentration of 1.1 micromol/L. CONCLUSIONS: Naftopidil seems to reduce prostate cancer incidence, possibly by inducing apoptosis, preferentially in cancer cells, and blocking transforming growth factor-beta signaling.

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[869]

**TÍTULO / TITLE:** - Editorial Comment from Dr Murtola to Reduction of prostate cancer incidence by naftopidil, an alpha1-adrenoceptor antagonist and transforming growth factor-beta signaling inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Urol. 2013 Apr 21. doi: 10.1111/iju.12175.

●●Enlace al texto completo (gratis o de pago) [1111/iju.12175](#)

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[870]

**TÍTULO / TITLE:** - Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Med. 2013 Apr;2(2):234-42. doi: 10.1002/cam4.71. Epub 2013 Mar 6.

●●Enlace al texto completo (gratis o de pago) [1002/cam4.71](#)

**AUTORES / AUTHORS:** - Liu Y; Starr MD; Bulusu A; Pang H; Wong NS; Honeycutt W; Amara A; Hurwitz HI; Nixon AB

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Duke University Medical Center Durham, North Carolina.

**RESUMEN / SUMMARY:** - A novel combination of capecitabine, oxaliplatin, and bevacizumab was evaluated in colorectal cancer patients enrolled in a phase II clinical trial. In this retrospective analysis, plasma samples from patients receiving capecitabine, oxaliplatin, and bevacizumab were analyzed to investigate biomarkers of clinical benefit. Forty-one protein biomarkers were tested in 38 patients at baseline and after two cycles of drug administration. Correlations among analytes were evaluated by Spearman analysis. Analyte levels at baseline and changes on-treatment were correlated with progression-free survival (PFS) and overall survival (OS) by univariate analysis. Multivariate analyses were determined using the Cox proportional hazard model. Time to event analyses were evaluated by Kaplan-Meier analysis and compared by log-rank test. Baseline levels of vWF and Ang-2 significantly correlated with PFS, while levels of VCAM-1, vWF, TSP-2, IL-8, MMP-2, and Ang-2 correlated with OS ( $P < 0.05$ ). The fold change of IGF-1 levels from baseline to the end of cycle 2 was correlated with PFS, while fold changes of Ang-2, TSP-2, and TGF-beta2 correlated with OS. A baseline signature of Ang-2, IGFBP-3, IL-6, and VCAM-1 identified a low-risk and high-risk group of patients (OS: 33.9 months vs. 18.1 months, respectively,  $P = 0.016$ ). For treatment-related changes, a signature consisting of Ang-2, E-Cadherin, IL-6, MCP-1, OPN, and TGF-beta1 was able to stratify patients into high- and low-risk groups (PFS: 7.7 months vs. 15.5 months,  $P = 0.004$ ). Multiplex analysis of patient plasma in this trial identified several baseline- and treatment-related biomarkers associated with clinical outcome. These findings merit further exploration in larger, controlled clinical trials.

[871]

**TÍTULO / TITLE:** - Attitudes of patients with cancer about personalized medicine and somatic genetic testing.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Oncol Pract. 2012 Nov;8(6):329-35, 2 p following 335. doi: 10.1200/JOP.2012.000626. Epub 2012 Aug 7.

●●Enlace al texto completo (gratis o de pago) [1200/JOP.2012.000626](#)

**AUTORES / AUTHORS:** - Gray SW; Hicks-Courant K; Lathan CS; Garraway L; Park ER; Weeks JC

**INSTITUCIÓN / INSTITUTION:** - Center for Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, LW 633, Boston, MA 02215, USA. [stacyw\\_gray@dfci.harvard.edu](mailto:stacyw_gray@dfci.harvard.edu)

**RESUMEN / SUMMARY:** - PURPOSE: Dramatic advances in genomic technology stand to revolutionize cancer care; however, little is known about patients' understanding and acceptance of personalized medicine and widespread genetic testing (GT). PATIENTS AND METHODS: We conducted a formative, semi-structured interview study with a random sample of patients with lung,

colorectal, and breast cancers to assess awareness of personalized medicine and GT and attitudes about somatic GT. Willingness to undergo GT was elicited through hypothetical scenarios. RESULTS: Sixty-nine patients participated; 71% were women; 42% were black; median age was 59 years; and 42% had an education level  $\geq$  college. We found that a majority of patients either were not aware of the term “personalized medicine” or defined it in unexpected ways. Although many patients identified relevant benefits of somatic testing (eg, informs treatment), many patients also expressed significant concerns (ie, psychological harm and discrimination). A majority of patients expressed a willingness to undergo somatic (predictive, 96%, prognostic, 93%) and germline (cancer risk without incidental information, 87%; cancer risk with incidental information, 81%; pharmacogenetic, 91%) testing; however, far fewer patients expressed a willingness to undergo full genome sequencing (62%). Reluctance was attributed to concerns over incidental findings, information overload, and the lack of a clear benefit. CONCLUSION: Many patients relayed misunderstandings about somatic testing and a reluctance to undergo full sequencing; oncologists must carefully consider how they present testing to patients so that concerns over discrimination and psychological harm do not hinder test uptake. More work is needed to identify effective ways to communicate complex genomic concepts to patients and research participants.

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[872]

**TÍTULO / TITLE:** - A Quantitative Deficiency in Peripheral Blood Vgamma9Vdelta2 Cells Is a Negative Prognostic Biomarker in Ovarian Cancer Patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 23;8(5):e63322. doi: 10.1371/journal.pone.0063322. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063322](#)

**AUTORES / AUTHORS:** - Thedrez A; Lavoue V; Dessarthe B; Daniel P; Henno S; Jaffre I; Leveque J; Catros V; Cabillic F

**INSTITUCIÓN / INSTITUTION:** - Unite Mixte de Recherche Institut National de la Sante Et de la Recherche Medicale 991, Universite de Rennes 1, Rennes, France ; Faculte de medecine, Universite de Rennes 1, Rennes, France.

**RESUMEN / SUMMARY:** - Vgamma9Vdelta2 cells are cytotoxic T cells that are able to recognize epithelial ovarian carcinoma (EOC) cells. Therefore, Vgamma9Vdelta2 cell-based adoptive transfer is an attractive therapy for EOC. However, the inefficient ex vivo expansion after specific stimulation of Vgamma9Vdelta2 cells from some patients and the relationships between Vgamma9Vdelta2 cells and clinical course of EOC are issues that remain to be clarified. Herein, peripheral blood mononuclear cells (PBMCs) from 60 EOC patients were stimulated with bromohydrin pyrophosphate (BrHPP) or zoledronate, which are specific agonists of Vgamma9Vdelta2 cells. The

compounds differed in their efficacies to induce ex vivo Vgamma9Vdelta2 PBMC expansion, but 16/60 samples remained inefficiently expanded with both stimuli. Interestingly, the Vgamma9Vdelta2 cells in these low-responding PBMCs displayed before expansion (ex vivo PBMCs) an altered production of the pro-inflammatory cytokines IFN-gamma and TNF-alpha, a decreased naive fraction and a reduced frequency. No evidence of an involvement of CD4(+)CD25(+)Foxp3(+) regulatory cells was observed. Importantly, our data also demonstrate that a Vgamma9Vdelta2 cell frequency of 0.35% or less in EOC PBMCs could be used to predict low responses to both BrHPP and zoledronate. Moreover, our data highlight that such a deficiency is not correlated with advanced EOC stages but is associated with more refractory states to platinum-based chemotherapy and is an independent predictor of shorter disease-free survival after treatment. These results are the first to suggest a potential contribution of Vgamma9Vdelta2 cells to the anti-tumor effects of chemotherapeutic agents and they strengthen interest in strategies that might increase Vgamma9Vdelta2 cells in cancer patients.

[873]

**TÍTULO / TITLE:** - Basigin-2 is the predominant basigin isoform that promotes tumor cell migration and invasion and correlates with poor prognosis in epithelial ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 Apr 8;11:92. doi: 10.1186/1479-5876-11-92.

●●Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-92](#)

**AUTORES / AUTHORS:** - Zhao SH; Wang Y; Wen L; Zhai ZB; Ai ZH; Yao NL; Wang L; Liu WC; Chen BL; Li Y; Yang H

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Xijing Hospital, The Fourth Military Medical University, Xi'an 710032, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Basigin, which has four isoforms, has been demonstrated to be involved in progression of various human cancers. The aim of this study was to examine the prognostic value of basigin-2 protein expression in epithelial ovarian cancer. Furthermore, the function of basigin-2 in ovarian cancer was further investigated in cell culture models. METHODS: Immunohistochemistry staining was performed to investigate basigin-2 expression in a total of 146 ovarian tissue specimens. Kaplan Meier analysis and Cox proportional hazards model were applied to assess the relationship between basigin-2 and progression-free survival (PFS) and overall survival (OS). Real-time PCR, RT-PCR and western blot were used to explore basigin-2, basigin-3 and basigin-4 expression in ovarian cancer cell lines and tissues. To evaluate possible contributions of basigin-2 to MMP secretion and cell migration and invasion, the overexpression vectors pcDNA3.1-basigin-2 and basigin-2 siRNA were transfected into HO-8910 and HO-8910 PM cells respectively. RESULTS: High basigin-2 expression was associated with lymph-

vascular space involvement, lymph node metastasis and poor prognosis of epithelial ovarian cancer. Multivariate analyses indicated that basigin-2 positivity was an independent prognostic factor for PFS ( $P = 0.006$ ) and OS ( $P = 0.019$ ), respectively. Overexpression of basigin-2 increased the secretion of MMP-2/9 and cancer cell migration and invasion of HO-8910 cells, whereas knockdown of basigin-2 reduced active MMP-2/9 production, migration and invasion of HO-8910 PM cells. CONCLUSIONS: The expression of basigin-2 might be an independent prognostic marker and basigin-2 inhibition would be a potential strategy for epithelial ovarian cancer patients, especially in inhibiting and preventing cancer cell invasion and metastasis.

[874]

**TÍTULO / TITLE:** - High expression of heat shock protein 90 is associated with tumor aggressiveness and poor prognosis in patients with advanced gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 26;8(4):e62876. doi: 10.1371/journal.pone.0062876. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062876](#)

**AUTORES / AUTHORS:** - Wang J; Cui S; Zhang X; Wu Y; Tang H

**INSTITUCIÓN / INSTITUTION:** - Department of Abdominal Surgery, Affiliated Oncologic Hospital of Guangzhou Medical College, Guangzhou, Guangdong, China.

**RESUMEN / SUMMARY:** - The heat shock protein 90 (HSP90) is overexpressed and highly associated with poor prognosis in many malignancies. However, the role of HSP90 in gastric cancer has not been thoroughly elucidated. The aim of this study is to investigate the relationship of HSP90 expression with clinicopathological parameters and prognosis in advanced gastric cancer, and estimate the alteration of HSP90 expression after neoadjuvant chemotherapy. HSP90 and matrix metalloproteinase 9 (MMP-9) antigen expression was evaluated by immunohistochemistry in 322 advanced gastric carcinoma samples. The relationships between HSP90 and clinicopathological parameters and prognosis were analyzed. The response of HSP90 level was assessed in chemotherapeutic effect in 54 patients received 1-2 cycles of neoadjuvant chemotherapy. The positive expression of HSP90 was found to be 69.6% in 322 advanced gastric carcinoma samples. HSP90 protein expression was significantly associated with depth invasion ( $P < 0.001$ ), lymph node metastasis ( $P < 0.001$ ) and stage of disease ( $P < 0.001$ ). The positive rates of HSP90 expression were higher in both prominent serosal invasion group ( $P < 0.001$ ) and lymph node metastasis group ( $P < 0.001$ ). Moreover, HSP90 was significantly correlated with MMP-9 among 322 gastric cancer tissues ( $P < 0.001$ ). In univariate and multivariate analyses, HSP90 was an independent

prognostic factor for both recurrence-free survival (RFS) and overall survival (OS). These results suggested that HSP90 may play an important role on tumor invasion, metastasis and prognosis, and might act as a promising target for prognostic prediction.

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[875]

**TÍTULO / TITLE:** - Expression of the IAP protein family acts cooperatively to predict prognosis in human bladder cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1278-1284. Epub 2013 Jan 23.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1150](#)

**AUTORES / AUTHORS:** - Chen X; Wang T; Yang D; Wang J; Li X; He Z; Chen F; Che X; Song X

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, P.R. China.

**RESUMEN / SUMMARY:** - The inhibitors of apoptosis (IAPs) are a group of anti-apoptotic factors in the apoptotic pathway that render cancer cells insensitive to apoptotic stimulation. Recently, several members of the IAP family have been investigated in the context of bladder cancer, and some of these have been associated with specific clinical and pathological tumor features, and with prognosis. These data suggested that the expression of an individual nuclear IAP has an important relationship with the progression of bladder cancer. To date, there are no studies concerning the overall tendencies of IAPs and their comparative therapeutic values in bladder cancer. In this study, we investigated the overall expression trends of the five tumor-related proteins, Survivin, cIAP1, cIAP2, XIAP and Livin, in normal bladder tissues and bladder cancer tissues. We classified and compared the gene expression data of these IAPs with the corresponding clinical and pathological tumor features, and with prognosis, in the development and progression of bladder cancer. The differences in IAP expression levels between archival bladder specimens from 36 normal controls and 105 patients who underwent surgery at our facility were examined using western blot analysis. The localization and expression level of each protein in low- and high-grade bladder cancer tissues were examined through immunohistochemistry. The cytoplasmic expression levels of each protein were scored as 0 (negative), +1 (weak), +2 (medium) or +3 (strong). The nuclear expression levels of cIAP1 and Survivin were scored as 0 (0%), +1 (1-25%), +2 (26-50%) or +3 (>50%). The results demonstrated that the expression of IAPs acted cooperatively to predict prognosis in human bladder cancer patients.

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[876]

**TÍTULO / TITLE:** - Clinical parameters predictive of outcomes in sorafenib-treated patients with advanced hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Liver Int. 2013 Apr 2. doi: 10.1111/liv.12168.

●●Enlace al texto completo (gratis o de pago) [1111/liv.12168](http://1111/liv.12168)

**AUTORES / AUTHORS:** - Cho JY; Paik YH; Lim HY; Kim YG; Lim HK; Min YW; Gwak GY; Choi MS; Lee JH; Koh KC; Paik SW; Yoo BC

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Sorafenib is an orally active multikinase inhibitor approved for the treatment of advanced hepatocellular carcinoma (HCC). However, clinical parameters that may predict the treatment outcomes in sorafenib-treated advanced HCC patients remains unknown. METHODS: A total of 99 advanced (BCLC C) HCC patients treated with sorafenib as an initial treatment modality from January 2007 to December 2011 were retrospectively reviewed. Overall survival was the primary endpoint for the analysis. Various clinical parameters including tumour stage and adverse effects to sorafenib were analysed. Univariate and multivariate analysis were carried out to identify clinical parameters predictive of the effect of sorafenib. RESULTS: There were 86 males and 13 females included in this study, with a median age of 53 years. The median overall survival was 91 days. Sixty-nine patients had Child-Pugh class A cirrhosis and 30 patients had Child-Pugh class B cirrhosis. Hepatitis B virus was the predominant cause of HCC (75.8%). Noted adverse effects were hand-foot syndrome, diarrhoea, fatigue, abdominal pain, nausea and stomatitis. The presence of hand-foot syndrome and diarrhoea and the absence of portal vein thrombosis and lymph node metastasis predicted a better overall survival in the multivariate analysis. Excluding the absence of lymph node metastasis, the same parameters were associated with a longer radiological time to progression. CONCLUSION: Advanced HCC patients treated with sorafenib who experienced hand-foot syndrome and diarrhoea showed better overall survival than patients without these side effects. These side effects may be used as clinical parameters predictive of sorafenib response in patients with HCC.

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[877]

**TÍTULO / TITLE:** - Activation of executioner caspases is a predictor of progression-free survival in glioblastoma patients: a systems medicine approach.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 May 16;4:e629. doi: 10.1038/cddis.2013.157.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.157](http://1038/cddis.2013.157)

**AUTORES / AUTHORS:** - Murphy AC; Weyhenmeyer B; Schmid J; Kilbride SM; Rehm M; Huber HJ; Senft C; Weissenberger J; Seifert V; Dunst M; Mittelbronn M; Kogel D; Prehn JH; Murphy BM

**INSTITUCIÓN / INSTITUTION:** - Centre for Systems Medicine, Department of Physiology and Medical Physics, St. Stephen's Green, Dublin, Ireland.

**RESUMEN / SUMMARY:** - Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults. GBM cells are highly resistant to apoptosis induced by antitumor drugs and radiotherapy resulting in cancer progression. We assessed whether a systems medicine approach, analysing the ability of tumor cells to execute apoptosis could be utilized to predict the response of GBM patients to treatment. Concentrations of the key proapoptotic proteins procaspase-3, procaspase-9, Smac and Apaf-1 and the antiapoptotic protein XIAP were determined in a panel of GBM cell lines and GBM patient tumor resections. These values were used as input for APOPTO-CELL, a systems biological based mathematical model built to predict cellular susceptibility to undergo caspase activation. The modeling was capable of accurately distinguishing between GBM cells that die or survive in response to treatment with temozolomide in 10 of the 11 lines analysed. Importantly the results obtained using GBM patient samples show that APOPTO-CELL was capable of stratifying patients according to their progression-free survival times and predicted the ability of tumor cells to support caspase activation in 16 of the 21 GBM patients analysed. Calculating the susceptibility to apoptosis execution may be a potent tool in predicting GBM patient therapy responsiveness and may allow for the use of APOPTO-CELL in a clinical setting.

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[878]

**TÍTULO / TITLE:** - Epigenetic Silencing of the Proapoptotic Gene BIM in Anaplastic Large Cell Lymphoma through an MeCP2/SIN3a Deacetylating Complex.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neoplasia. 2013 May;15(5):511-22.

**AUTORES / AUTHORS:** - Piazza R; Magistroni V; Mogavero A; Andreoni F; Ambrogio C; Chiarle R; Mologni L; Bachmann PS; Lock RB; Collini P; Pelosi G; Gambacorti-Passerini C

**INSTITUCIÓN / INSTITUTION:** - Department of Health Sciences, University of Milano, Bicocca, Monza, Italy.

**RESUMEN / SUMMARY:** - BIM is a proapoptotic member of the Bcl-2 family. Here, we investigated the epigenetic status of the BIM locus in NPM/ALK+ anaplastic large cell lymphoma (ALCL) cell lines and in lymph node biopsies from NPM/ALK+ ALCL patients. We show that BIM is epigenetically silenced in cell lines and lymph node specimens and that treatment with the deacetylase inhibitor trichostatin A restores the histone acetylation, strongly upregulates BIM expression, and induces cell death. BIM silencing occurs through recruitment of MeCP2 and the SIN3a/histone deacetylase 1/2 (HDAC1/2) corepressor complex. This event requires BIM CpG methylation/demethylation with 5-azacytidine that leads to detachment of the MeCP2 corepressor complex and reacetylation of the histone tails. Treatment with the ALK inhibitor PF2341066 or with an inducible shRNA targeting NPM/ALK does not restore BIM locus reacetylation; however, enforced expression of NPM/ALK in an NPM/ALK-negative cell line

significantly increases the methylation at the BIM locus. This study demonstrates that BIM is epigenetically silenced in NPM/ALK-positive cells through recruitment of the SIN3a/HDAC1/2 corepressor complex and that NPM/ALK is dispensable to maintain BIM epigenetic silencing but is able to act as an inducer of BIM methylation.

[879]

**TÍTULO / TITLE:** - Phase II Study of Satraplatin and Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer: A Pharmacogenetic Assessment of Outcome and Toxicity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Genitourin Cancer. 2013 May 16. pii: S1558-7673(13)00053-0. doi: 10.1016/j.clgc.2013.04.007.

●●Enlace al texto completo (gratis o de pago) [1016/j.clgc.2013.04.007](http://1016/j.clgc.2013.04.007)

**AUTORES / AUTHORS:** - Figg WD; Chau CH; Madan RA; Gulley JL; Gao R; Sissung TM; Spencer S; Beatson M; Aragon-Ching J; Steinberg SM; Dahut WL

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Branch, Center for Cancer Research (CCR), National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD. Electronic address: [figgw@helix.nih.gov](mailto:figgw@helix.nih.gov).

**RESUMEN / SUMMARY:** - BACKGROUND: We assessed the effect of excision repair cross-complementing group 1 (ERCC1) and x-ray cross-complementing group 1 (XRCC1) gene polymorphisms on treatment outcomes with satraplatin and prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based therapy. PATIENTS AND METHODS: Twenty-four patients were enrolled in this single arm study. The primary objective was to determine if the presence of ERCC1 Asn118Asn (N118N, 500C>T, rs11615) and XRCC1 Arg399Gln (R399Q, 1301G>A, rs25487) genetic variants might be associated with an impact on progression-free survival (PFS); secondary objectives included overall response, survival, and toxicity. RESULTS: After population stratification by race, white patients carrying heterozygous or variant genotypes at the ERCC1 C>T locus had a >3-fold longer median PFS (5.8 vs. 1.8 months; 2P = .18, adjusted) and 5-fold longer median overall survival (OS) (15.7 vs. 3.2 months; 2P = .010, adjusted) than did patients carrying only wild-type alleles. For the XRCC1 G>A variant, without regard to race, patients carrying the wild-type GG alleles had a longer PFS (9.3 months) than those carrying GA or AA alleles (2.7 months; 2P = .02). Similarly, those carrying GG alleles did not reach median OS, whereas those carrying GA or AA alleles had a median OS of 9.6 months (2P = .12, adjusted). Multivariable analysis by using Cox proportional hazards modeling demonstrated that only XRCC1 was associated with PFS. CONCLUSIONS: To our knowledge, this is the first prospective study to date in patients with metastatic castration-resistant prostate cancer that describes predictive

germline polymorphisms of ERCC1 and XRCC1 for assessing the clinical activity of satraplatin.

[880]

**TÍTULO / TITLE:** - Characterization and Prognostic Value of Mutations in Exons 5 and 6 of the p53 Gene in Patients with Colorectal Cancers in Central Iran.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gut Liver. 2013 May;7(3):295-302. doi: 10.5009/gnl.2013.7.3.295. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [5009/gnl.2013.7.3.295](#)

**AUTORES / AUTHORS:** - Golmohammadi R; Namazi MJ; Nikbakht M; Salehi M; Derakhshan MH

**INSTITUCIÓN / INSTITUTION:** - Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran.

**RESUMEN / SUMMARY:** - BACKGROUND/AIMS: We aimed to investigate the relationships among various mutations of the p53 gene and their protein products, histological characteristics, and disease prognosis of primary colorectal cancer in Isfahan, central Iran. METHODS: Sixty-one patients with colorectal adenocarcinoma were enrolled in the study. Mutations of the p53 gene were detected by single-stranded conformation polymorphism and DNA sequencing. The protein stability was evaluated by immunohistochemistry. Patients were followed up to 48 months. RESULTS: Twenty-one point mutations in exons 5 and 6 were detected in the tumor specimens of 14 patients (23%). Of those, 81% and 9.5% were missense and nonsense mutations, respectively. There were also two novel mutations in the intronic region between exons 5 and 6. In 11 mutated specimens, protein stability and protein accumulation were identified. There was a relationship between the type of mutation and protein accumulation in exons 5 and 6 of the p53 gene. The presence of the mutation was associated with an advanced stage of cancer (trend,  $p < 0.009$ ). Patients with mutated p53 genes had significantly lower survival rates than those with wild type p53 genes ( $p < 0.01$ ). CONCLUSIONS: Mutations in exons 5 and 6 of the p53 gene are common genetic alterations in colorectal adenocarcinoma in central Iran and are associated with a poor prognosis of the disease.

[881]

**TÍTULO / TITLE:** - Cost-effectiveness analysis comparing degarelix with leuprolide in hormonal therapy for patients with locally advanced prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Rev Pharmacoecon Outcomes Res. 2013 Apr;13(2):261-70. doi: 10.1586/erp.13.13.

●●Enlace al texto completo (gratis o de pago) [1586/erp.13.13](#)

**AUTORES / AUTHORS:** - Hatoum HT; Crawford ED; Nielsen SK; Lin SJ; Marshall DC

**INSTITUCIÓN / INSTITUTION:** - Hind T Hatoum & Company, 155 N Harbor Drive, 1912, Chicago, IL 60601, USA. [hthatoum@sbcglobal.net](mailto:hthatoum@sbcglobal.net)

**RESUMEN / SUMMARY:** - Degarelix, approved in the USA in 2008, is a gonadotropin-releasing hormone antagonist, representing one of the latest additions to androgen deprivation therapy (ADT). ADT is used as first-line therapy for locally advanced or metastatic prostate cancer with the aim to reduce testosterone to castrate levels. Like other gonadotropin-releasing hormone-antagonists, degarelix treatment results in rapid decrease in luteinizing hormone, follicle-stimulating hormone and testosterone levels without the associated risk of flare. Using one registration trial for degarelix with leuprolide as the active control, a cost-effectiveness analysis with a Markov model and a 20-year time horizon found the incremental cost-effectiveness ratio for degarelix to be US\$245/quality-adjusted life years. Degarelix provides a cost-effective treatment for ADT among patients with locally advanced prostate cancer.

[882]

**TÍTULO / TITLE:** - A myeloma cell line established from a patient refractory to thalidomide therapy revealed high-risk cytogenetic abnormalities and produced vascular endothelial growth factor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood Cancer J. 2013 May 17;3:e115. doi: 10.1038/bcj.2013.13.

●●Enlace al texto completo (gratis o de pago) [1038/bcj.2013.13](http://1038/bcj.2013.13)

**AUTORES / AUTHORS:** - Hattori Y; Du W; Yamada T; Ichikawa D; Matsunami S; Matsushita M

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Physiology and Therapeutics, Keio University Faculty of Pharmacy, Tokyo, Japan.

[883]

**TÍTULO / TITLE:** - Prognostic comparison of the proliferation markers mitotic activity index, phosphohistone H3, Ki67, steroid receptors, HER2, high molecular weight cytokeratins and classical prognostic factors in T1-2N0M0 breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pol J Pathol. 2013 Mar;64(1):1-8.

**AUTORES / AUTHORS:** - Gudlaugsson E; Klos J; Skaland I; Janssen EA; Smaaland R; Feng W; Shao Z; Malpica A; Baak JP

**INSTITUCIÓN / INSTITUTION:** - Jan P.A. Baak, MD, PhD, FRCPATH(Hon), FICP(Hon), Department of Pathology, Stavanger University Hospital, Armauer Hansen Rd 20, N-4068 Stavanger, Norway, tel. +47 51 51 93 78, fax +47 51 51 99 10, e-mail: [jpabaak47@yahoo.com](mailto:jpabaak47@yahoo.com).

**RESUMEN / SUMMARY:** - The proliferation factors: mitotic activity index (MAI), phosphohistone H3 (PPH3) and Ki67 have strong prognostic value in early breast cancer but their independent value to each other and other prognostic factors has not been evaluated. In 237 T1-2N0M0 breast cancers without systemic adjuvant treatment, formalized MAI assessment and strictly standardized, fully automated quantitative immunohistochemistry (IHC) for Ki67, PPH3, estrogen (ER) and progesterone receptor (PR), HER2, cytokeratins-5/6 and -14, and automated digital image analysis (DIA) for measuring PPH3 and Ki67 were performed. Section thickness was measured to further control IHC measurements. All features were measured in the periphery of tumors. The different proliferation assessments and other well-established clinicopathological and biomarker prognostic factors were compared. DIA-Ki67 added prognostically to PPH3. None of the other biomarkers or clinicopathological variables added prognostically to this PPH3/Ki67 combination. However, when PPH3 is replaced by MAI the prognostic value is nearly the same. In early operable node negative breast cancer without adjuvant systemic treatment, Ki67 with a threshold of 6.5% assessed by digital image analysis in the periphery of the tumor is prognostically strong. The combination of either PPH3/Ki67 or MAI/Ki67 overshadowed the prognostic value of all other features including Ki67 alone.

[884]

**TÍTULO / TITLE:** - Impact of serum C-reactive protein level on the prognosis of patients with hepatocellular carcinoma undergoing TACE.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Mol Hepatol. 2013 Mar;19(1):70-7. doi: 10.3350/cmh.2013.19.1.70. Epub 2013 Mar 25.

●●Enlace al texto completo (gratis o de pago) [3350/cmh.2013.19.1.70](#)

**AUTORES / AUTHORS:** - Jun CH; Ki HS; Lee KH; Park KJ; Park SY; Cho SB; Park CH; Joo YE; Kim HS; Choi SK; Rew JS

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea.

**RESUMEN / SUMMARY:** - BACKGROUND/AIMS: The aim of this study was to determine the relationship between serum CRP levels and the prognosis of hepatocellular carcinoma (HCC) patients. METHODS: HCC patients who underwent the first session of transcatheter arterial chemoembolization (TACE) between January 2005 and December 2009 (n=211) were analyzed retrospectively. The patients were divided into two groups: high C-reactive protein (CRP;  $\geq 1$  mg/dL, n=51) and low CRP (<1 mg/dL, n=160). They were followed for a mean of 22.44 months and their clinicoradiological variables and overall survival were compared. RESULTS: There were significant differences between the two groups in regard to tumor type, tumor-progression-free survival, 10-month mortality, white blood cell (WBC) count, tumor size, and

TNM stage. Multivariate analysis revealed that a high serum CRP level was independently associated with tumor size and tumor type. Subgroup analysis of CRP groups according to tumor size demonstrated that a high serum level of CRP was significantly associated with poorly defined (diffuse) tumor type in the tumor size <5 cm group [hazard ratio (HR)=4.81, P=0.018]. A Lipiodol dose exceeding 7 mL (HR=5.55, P=0.046) and the 10-month mortality (HR=7.693, P=0.004) were significantly associated with high serum CRP level in the group of patients with a tumor size of  $\geq$ 5 cm. In addition, subgroup analysis of matched CRP according to TNM stage revealed that elevated serum CRP was independently associated with tumor type, WBC count, and tumor progression-free survival. CONCLUSIONS: A high serum CRP level is associated with large tumors and a poorly defined tumor type, and is significantly associated with 10-month mortality in patients with large HCC (size  $\geq$ 5 cm) who undergo TACE.

[885]

**TÍTULO / TITLE:** - Tumor-associated lymphocytes predict response to neoadjuvant chemotherapy in breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Breast Cancer. 2013 Mar;16(1):32-9. doi: 10.4048/jbc.2013.16.1.32. Epub 2013 Mar 31.

●●Enlace al texto completo (gratis o de pago) [4048/jbc.2013.16.1.32](#)

**AUTORES / AUTHORS:** - Lee HJ; Seo JY; Ahn JH; Ahn SH; Gong G

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - PURPOSE: Tumor-associated lymphocyte numbers in breast cancer have been suggested as a new independent predictor of response to neoadjuvant chemotherapy in breast cancer patients. We therefore evaluated the relationship between pathologic complete response (pCR) and tumor-associated lymphocytes in tumors of such patients. METHODS: Between 2000 and 2009, we retrospectively evaluated 175 patients with primary breast cancer treated with neoadjuvant chemotherapy, followed by definitive surgical resection. Peritumoral lymphocytic infiltration (LI) and CD3(+), CD8(+), and forkhead box P3 (FOXP3)(+) lymphocytes were assessed in pretreatment biopsy specimens. RESULTS: Nineteen (11%) patients achieved pCR. An elevated LI, CD3(+), CD8(+), or FOXP3(+) lymphocytic infiltration; lower clinical T stage; human epidermal growth factor receptor 2 overexpression; and herceptin-based treatment were all significantly associated with pCR. Through a multivariate analysis, LI (odds ratio [OR], 1.26; p=0.024), clinical T stage (OR, 3.06; p=0.041), and the use of a herceptin-based regimen (OR, 4.95; p=0.004) were all significant independent predictors of pCR. Significantly higher numbers of tumor-associated lymphocytes and CD3(+), CD8(+), and FOXP3(+) T-cells were observed in the following: high-grade tumors, tumors of positive nodal status, and tumors negative for hormone receptors. CONCLUSION: Tumor-associated lymphocytes are significantly associated with pCR, suggesting that

tumor-associated lymphocytes may be an important pathological factor predicting a response to neoadjuvant chemotherapy in breast cancer patients.

[886]

**TÍTULO / TITLE:** - Activity of histone deacetylase inhibitors and an Aurora kinase inhibitor in BCR-ABL-expressing leukemia cells: Combination of HDAC and Aurora inhibitors in BCR-ABL-expressing cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Cell Int. 2013 Apr 4;13(1):32. doi: 10.1186/1475-2867-13-32.

●●Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-32](#)

**AUTORES / AUTHORS:** - Okabe S; Tauchi T; Tanaka Y; Kimura S; Maekawa T; Ohyashiki K

**INSTITUCIÓN / INSTITUTION:** - First Department of Internal Medicine, Tokyo Medical University, Tokyo 160-0023, Japan. [okabe@tokyo-med.ac.jp](mailto:okabe@tokyo-med.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The use of imatinib, an ABL tyrosine kinase inhibitor, has led to a dramatic change in the management of BCR-ABL-positive leukemia patients. However, resistance to imatinib mediated by mutations in the BCR-ABL domain has become a major problem in the treatment of these patients. METHODS: In the present study, we examined the activity of histone deacetylase (HDAC) inhibitors in combination with an Aurora kinase inhibitor in BCR-ABL-expressing cells. RESULTS: We found the HDAC inhibitors vorinostat and/or pracinostat (SB939) induced apoptosis in BCR-ABL-expressing cells. Additionally, HDAC inhibitors reduced levels of Aurora A and B protein. An Aurora kinase inhibitor, tozasertib (VX-680), inhibited growth, promoted pro-apoptotic activity, reduced the phosphorylation of BCR-ABL and Crk-L, and activated caspase-3 and poly (ADP-ribose) polymerase (PARP) in BCR-ABL-positive cells. Moreover, after treatment with tozasertib, HDAC protein expression was decreased. Combination of vorinostat or pracinostat with tozasertib had a synergistic inhibitory effect on the proliferation of T3151 cells. Phosphorylation of Crk-L decreased, and PARP activation increased after treatment with vorinostat or pracinostat and tozasertib. Moreover, combination of vorinostat or pracinostat and tozasertib significantly increased the extent of apoptosis in primary chronic myeloid leukemia cells. CONCLUSIONS: This study demonstrated that combination of HDAC and Aurora inhibitors was highly effective against BCR-ABL-expressing cells.

[887]

**TÍTULO / TITLE:** - Hematopoietic stem cell transplant versus chemotherapy plus tyrosine kinase inhibitor in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hematol Oncol Stem Cell Ther. 2013 Mar;6(1):34-41. doi: 10.1016/j.hemonc.2013.03.001. Epub 2013 Mar 26.

- Enlace al texto completo (gratis o de pago)

[1016/j.hemonc.2013.03.001](http://1016/j.hemonc.2013.03.001)

**AUTORES / AUTHORS:** - Salami K; Alkayed K; Halalsheh H; Hussein AA; Riziq M; Madanat F

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, King Hussein Cancer Center, Amman, Jordan.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) remained until recently the molecular genetic abnormality associated with the worst outcome. Hematopoietic stem cell transplant (HSCT) was considered the treatment of choice, however, recent data have indicated that chemotherapy plus tyrosine kinase inhibitor (TKI) maybe an alternative effective therapy. **METHODS:** We conducted a retrospective analysis of children (<18years) with Ph+ ALL who were treated at King Hussein Cancer Center (KHCC) from January 2003 till December 2011. **RESULTS:** Over a 9year period, 411 children were diagnosed and treated for ALL at KHCC. Twenty three (6.6%) had Ph+ ALL; 16 males and 7 females. Median age at diagnosis was 9.5years (range 1.67-17). The median white blood cell count was  $58.6 \times 10^3 / \mu\text{L}$  (range 1.6-459). Twelve patients underwent HSCT from a full matched related donor; and 10 were treated with intensive chemotherapy plus TKI (imatinib). Those who underwent HSCT were significantly older ( $P=0.004$ ) and had a higher leukocyte count at diagnosis ( $P=0.53$ ). After a median follow up of 42.2months (range 12.7-107), the estimated 5year event free survival (EFS) and overall survival (OS) were 75% and 91.6%, respectively, for those who underwent HSCT as primary therapy and 49.3% and 83.3%, respectively, for those treated with chemotherapy plus imatinib. There was no significant difference in EFS ( $P=0.98$ ) or OS ( $P=1$ ) between the two treatment modalities. **CONCLUSIONS:** Our results indicate that chemotherapy plus TKI may be a reasonable treatment option for some children with Ph+ ALL.

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[888]

**TÍTULO / TITLE:** - Predicting locoregional recurrence after neoadjuvant chemotherapy in patients with breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Adv Hematol Oncol. 2013 Mar;11(3):175-7.

**AUTORES / AUTHORS:** - Mamounas TP

**INSTITUCIÓN / INSTITUTION:** - Northeastern Ohio Universities College of Medicine, USA.

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[889]

**TÍTULO / TITLE:** - Bcl-2 Overexpression Inhibits Generation of Intracellular Reactive Oxygen Species and Blocks Adriamycin-induced Apoptosis in Bladder Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):895-901.

**AUTORES / AUTHORS:** - Kong CZ; Zhang Z

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, the First Hospital of China Medical University, Shenyang, China E-mail [kongchuize\\_cmu@yahoo.com.cn](mailto:kongchuize_cmu@yahoo.com.cn).

**RESUMEN / SUMMARY:** - Resistance to induction of apoptosis is a major obstacle for bladder cancer treatment. Bcl-2 is thought to be involved in anti-apoptotic signaling. In this study, we investigated the effect of Bcl-2 overexpression on apoptotic resistance and intracellular reactive oxygen species (ROS) generation in bladder cancer cells. A stable Bcl-2 overexpression cell line, BIU87-Bcl-2, was constructed from human bladder cancer cell line BIU87 by transfecting recombinant Bcl-2 [pcDNA3.1(+)-Bcl-2]. The sensitivity of transfected cells to adriamycin (ADR) was assessed by MTT assay. Apoptosis was examined by flow cytometry and acridine orange fluorescence staining. Intracellular ROS was determined using flow cytometry, and the activities of superoxide dismutase (SOD) and catalase (CAT) were also investigated by the xanthinoxidase and visible radiation methods using SOD and CAT detection kits. The susceptibility of BIU87-Bcl-2 cells to ADR treatment was significantly decreased as compared with control BIU87 cells. Enhanced expression of Bcl-2 inhibited intracellular ROS generation following ADR treatment. Moreover, the suppression of SOD and CAT activity induced by ADR treatment was blocked in the BIU87-Bcl-2 case but not in their parental cells. The overexpression of Bcl-2 renders human bladder cancer cells resistant to ADR-induced apoptosis and ROS might act as an important secondary messenger in this process.

[890]

**TÍTULO / TITLE:** - A novel therapeutic combination approach for treating multiple vemurafenib-induced keratoacanthomas: systemic acitretin and intralesional fluorouracil.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - JAMA. Acceso gratuito al texto completo.

●●Enlace a la Editora de la Revista <http://jama.ama-assn.org/search.dtl>

●●Cita: JAMA: <> Dermatol. 2013 Mar;149(3):279-81. doi: 10.1001/jamadermatol.2013.2583.

●●Enlace al texto completo (gratuito o de pago)

[1001/jamadermatol.2013.2583](#)

**AUTORES / AUTHORS:** - LaPresto L; Cranmer L; Morrison L; Erickson CP; Curiel-Lewandrowski C

**INSTITUCIÓN / INSTITUTION:** - College of Medicine, University of Arizona, Tucson, AZ, USA.

[891]

**TÍTULO / TITLE:** - Prognostic factors in resectable cholangiocarcinoma patients: Carcinoembryonic antigen, lymph node, surgical margin and chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Gastrointest Oncol. 2013 Apr 15;5(4):81-7. doi: 10.4251/wjgo.v5.i4.81.

●●Enlace al texto completo (gratis o de pago) [4251/wjgo.v5.i4.81](#)

**AUTORES / AUTHORS:** - Wirasorn K; Ngamprasertchai T; Chindaprasirt J; Sookprasert A; Khantikaew N; Pakkhem A; Ungarereevittaya P

**INSTITUCIÓN / INSTITUTION:** - Kosin Wirasorn, Thundon Ngamprasertchai, Jarin Chindaprasirt, Aumkhae Sookprasert, Department of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

**RESUMEN / SUMMARY:** - AIM: To evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors. METHODS: A retrospective study was conducted among newly-diagnosed cholangiocarcinoma patients from January 2009 to December 2011 who underwent curative resection in Srinakarind Hospital (a 1000-bed university hospital). Two hundred and sixty-three cholangiocarcinoma patients with good performance were enrolled. These patients had pathological reports with clear margins or microscopic margins. Prognostic factors which included clinical factors, serum liver function test as well as serum tumor makers at presentation, tumor data, and receiving adjuvant chemotherapy were determined by uni- and multivariate analysis. RESULTS: The median overall survival time was 17 mo (95%CI: 13.2-20.7); and 1-, 2-, and 3- year survival rates were 65.5%, 45.2% and 35.4%. Serum albumin levels, serum carcinoembryonic antigen (CEA) levels, staging classifications by American Joint Committee on cancer, pathological tumor staging, lymph node metastases, tumor grading, surgical margin status, and if adjuvant chemotherapy was administered, were shown to be significant prognostic factors of resectable cholangiocarcinoma by univariate analysis. Multivariate analysis, however, established that only abnormal serum CEA [hazard ratio (HR) 1.68; P = 0.027] and lymph node metastases (HR 2.27; P = 0.007) were significantly associated with a decrease in overall survival, while adjuvant chemotherapy (HR 0.71; P = 0.067) and surgical margin negative (HR 0.72; P = 0.094) tended to improve survival time. CONCLUSION: Serum CEA and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma.

[892]

**TÍTULO / TITLE:** - An Italian cost-effectiveness analysis of paclitaxel albumin (nab-paclitaxel) versus conventional paclitaxel for metastatic breast cancer patients: the COSTANza study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clinicoecon Outcomes Res. 2013 Apr 11;5:125-35. doi: 10.2147/CEOR.S41850. Print 2013.

●●Enlace al texto completo (gratis o de pago) [2147/CEOR.S41850](#)

**AUTORES / AUTHORS:** - Lazzaro C; Bordonaro R; Cognetti F; Fabi A; De Placido S; Arpino G; Marchetti P; Botticelli A; Pronzato P; Martelli E

**INSTITUCIÓN / INSTITUTION:** - Studio di Economia Sanitaria, Milan, Italy.

**RESUMEN / SUMMARY:** - **PURPOSE:** Paclitaxel albumin (nab-paclitaxel) is a nanoparticle albumin-bound paclitaxel formulation aimed at increasing therapeutic index in metastatic breast cancer. When compared to conventional paclitaxel, nab-paclitaxel has a reported longer time to progression, higher response, lower incidence of neutropenia, no need for premedication, shorter time of administration, and in pretreated metastatic breast cancer patients, extended overall survival. This study investigates the cost-effectiveness of nab-paclitaxel versus conventional paclitaxel for pretreated metastatic breast cancer patients in Italy. **MATERIALS AND METHODS:** A Markov model with progression-free, progressed, and dead states was developed to estimate costs, outcomes, and quality adjusted life years over 5 years from the Italian National Health Service viewpoint. Patients were assumed to receive nab-paclitaxel 260 mg/m<sup>2</sup> three times weekly or conventional paclitaxel 175 mg/m<sup>2</sup> three times weekly. Data on health care resource consumption was collected from a convenience sample of five Italian centers. Resources were valued at Euro (euro) 2011. Published utility weights were applied to health states to estimate the impact of response, disease progression, and adverse events on quality adjusted life years. Three sensitivity analyses tested the robustness of the base case incremental cost-effectiveness ratio (ICER). **RESULTS AND CONCLUSION:** Compared to conventional paclitaxel, nab-paclitaxel gains an extra 0.165 quality adjusted life years (0.265 life years saved) and incurs additional costs of euro2506 per patient treated. This translates to an ICER of euro15,189 (95% confidence interval: euro11,891-euro28,415). One-way sensitivity analysis underscores that ICER for nab-paclitaxel remains stable despite varying taxanes cost. Threshold analysis shows that ICER for nab-paclitaxel exceeds euro40,000 only if cost per mg of conventional paclitaxel is set to zero. Probabilistic sensitivity analysis highlights that nab-paclitaxel has a 0.99 probability to be cost-effective for a threshold value of euro40,000 and is the optimal alternative from a threshold value of euro16,316 onwards. Based on these findings, nab-paclitaxel can be considered highly cost-effective when compared to the acceptability range for ICER proposed by the Italian Health Economics Association (euro25,000-euro40,000).

[893]

**TÍTULO / TITLE:** - Weekly intravenous nanoparticle albumin-bound paclitaxel for elderly patients with stage IV non-small-cell lung cancer: a series of 20 cases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biomed Res. 2012 May;26(3):159-64. doi: 10.7555/JBR.26.20110106. Epub 2012 May 20.

●●Enlace al texto completo (gratis o de pago) [7555/JBR.26.20110106](#)

**AUTORES / AUTHORS:** - Zheng Q; Yao Y; Nan K

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, the First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China.

**RESUMEN / SUMMARY:** - The purpose of this study was to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel as a rescue regimen in the treatment of patients with advanced non-small-cell lung cancer. We retrospectively reviewed the medical records of 20 patients with stage IV non-small-cell lung cancer. The patients had progressive disease after standard antitumor therapy and subsequently received intravenous albumin-bound paclitaxel at the dose of 100 mg/m<sup>2</sup> in weekly schedule. Cumulative findings showed that the overall response rate was 30.0%, the disease control rate amounted to 40%, and the 1 year survival rate was 30%. In addition, the median time to progression and the median survival time reached 5 and 10 months, respectively. Meanwhile, no severe hypersensitivity reactions and grade 4 adverse effects were reported. In summary, weekly-administered albumin-bound paclitaxel seems to be an effective and safe regimen for elderly patients with stage IV non-small-cell lung cancer who were refractory to conventional therapy.

[894]

**TÍTULO / TITLE:** - Changes in Gene Expression Profiling of Apoptotic Genes in Neuroblastoma Cell Lines upon Retinoic Acid Treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 1;8(5):e62771. doi: 10.1371/journal.pone.0062771. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062771](http://1371/journal.pone.0062771)

**AUTORES / AUTHORS:** - Celay J; Blanco I; Lazcoz P; Rotinen M; Castresana JS; Encio I

**INSTITUCIÓN / INSTITUTION:** - Department of Health Sciences, Public University of Navarra, Pamplona, España.

**RESUMEN / SUMMARY:** - To determine the effect of retinoic acid (RA) in neuroblastoma we treated RA sensitive neuroblastoma cell lines with 9-cis RA or ATRA for 9 days, or for 5 days followed by absence of RA for another 4 days. Both isomers induced apoptosis and reduced cell density as a result of cell differentiation and/or apoptosis. Flow cytometry revealed that 9-cis RA induced apoptosis more effectively than ATRA. The expression profile of apoptosis and survival pathways was cell line specific and depended on the isomer used.

[895]

**TÍTULO / TITLE:** - TTC5 is required to prevent apoptosis of acute myeloid leukemia stem cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Apr 4;4:e573. doi: 10.1038/cddis.2013.107.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.107](https://doi.org/10.1038/cddis.2013.107)

**AUTORES / AUTHORS:** - Lynch JT; Somerville TD; Spencer GJ; Huang X; Somerville TC

**INSTITUCIÓN / INSTITUTION:** - Cancer Research UK Leukaemia Biology Laboratory, Paterson Institute for Cancer Research, The University of Manchester, Manchester, UK.

**RESUMEN / SUMMARY:** - Using a screening strategy, we identified the tetratricopeptide repeat (TPR) motif protein, Tetratricopeptide repeat domain 5 (TTC5, also known as stress responsive activator of p300 or Strap) as required for the survival of human acute myeloid leukemia (AML) cells. TTC5 is a stress-inducible transcription cofactor known to interact directly with the histone acetyltransferase EP300 to augment the TP53 response. Knockdown (KD) of TTC5 induced apoptosis of both murine and human AML cells, with concomitant loss of clonogenic and leukemia-initiating potential; KD of EP300 elicited a similar phenotype. Consistent with the physical interaction of TTC5 and EP300, the onset of apoptosis following KD of either gene was preceded by reduced expression of BCL2 and increased expression of pro-apoptotic genes. Forced expression of BCL2 blocked apoptosis and partially rescued the clonogenic potential of AML cells following TTC5 KD. KD of both genes also led to the accumulation of MYC, an acetylation target of EP300, and the form of MYC that accumulated exhibited relative hypoacetylation at K148 and K157, residues targeted by EP300. In view of the ability of excess cellular MYC to sensitize cells to apoptosis, our data suggest a model whereby TTC5 and EP300 cooperate to prevent excessive accumulation of MYC in AML cells and their sensitization to cell death. They further reveal a hitherto unappreciated role for TTC5 in leukemic hematopoiesis.

[896]

**TÍTULO / TITLE:** - Usefulness of Serum Carcinoembryonic Antigen (CEA) in evaluating response to chemotherapy in patients with advanced non small-cell lung cancer: a prospective cohort study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 22;13(1):254.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-254](https://doi.org/10.1186/1471-2407-13-254)

**AUTORES / AUTHORS:** - Arrieta Rodriguez OG; Villarreal-Garza C; Martinez-Barrera L; Morales M; Dorantes-Gallareta Y; Pena-Curiel O; Contreras-Reyes S; Macedo-Perez EO; Alatorre-Alexander J

**RESUMEN / SUMMARY:** - BACKGROUND: High serum carcinoembryonic antigen (CEA) levels are an independent prognostic factor for recurrence and survival in patients with non-small cell lung cancer (NSCLC). Its role as a predictive marker of treatment response has not been widely characterized. METHODS: 180 patients with advanced NSCLC (stage IIIB or Stage IV), who had an elevated CEA serum level (>10 ng/ml) at baseline and who had no more than one previous chemotherapy regimen, were included. CEA levels were measured

after two treatment cycles of platinum based chemotherapy (93%) or a tyrosine kinase inhibitor (7%). We evaluate the change in serum CEA levels and the association with response measured by RECIST criteria. RESULTS: After two chemotherapy cycles, the patients who achieved an objective response (OR, 28.3%) had a reduction of CEA levels of 55.6% (95%CI [box drawings light horizontal]64.3 to [box drawings light horizontal]46.8) compared to its basal level, with an area under the ROC curve (AURC) of 0.945 (95%CI 0.91-0.99), and a sensitivity and specificity of 90.2 and 89.9%, respectively, for a CEA reduction of  $\geq 14\%$ . Patients that achieved a decrease in CEA levels  $\geq 14\%$  presented an overall response in 78% of cases, stable disease in 20.3% and progression in 1.7%, while patients that did not attain a reduction  $\geq 14\%$  had an overall response of 4.1%, stable disease of 63.6% and progression of 32.2% ( $p < 0.001$ ). Patients with stable (49.4%) and progressive disease (22.2%) had an increase of CEA levels of 9.4% (95%CI 1.5-17.3) and 87.5% (95%CI 60.9-114) from baseline, respectively ( $p < 0.001$ ). The AURC for progressive disease was 0.911 (95%CI 0.86-0.961), with sensitivity and specificity of 85 and 15%, respectively, for a CEA increase of  $\geq 18\%$ . PFS was longer in patients with a  $\geq 14\%$  reduction in CEA (8.7 vs. 5.1 months,  $p < 0.001$ ). Neither reduction of CEA nor OR were predictive of OS. CONCLUSIONS: A CEA level reduction is a sensitive and specific marker of OR, as well as a sensitive indicator for progression to chemotherapy in patients with advanced NSCLC who had an elevated CEA at baseline and had received no more than one chemotherapy regimen. A 14% decrease in CEA levels is associated with a better PFS.

[897]

**TÍTULO / TITLE:** - Association of Genetic Markers in the BCL-2 Family of Apoptosis-Related Genes with Endometrial Cancer Risk in a Chinese Population.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 23;8(4):e60915. doi: 10.1371/journal.pone.0060915. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060915](http://1371/journal.pone.0060915)

**AUTORES / AUTHORS:** - Dorjgochoo T; Xiang YB; Long J; Shi J; Deming S; Xu WH; Cai H; Cheng J; Cai Q; Zheng W; Shu XO

**INSTITUCIÓN / INSTITUTION:** - Division of Epidemiology, Department of Medicine and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee, United States of America.

**RESUMEN / SUMMARY:** - BACKGROUND: In vitro studies have demonstrated the role of the BCL-2 family of genes in endometrial carcinogenesis. The role of genetic variants in BCL-2 genes and their interactions with non-genetic factors in the development of endometrial cancer has not been investigated in epidemiological studies. PATIENTS AND METHODS: We examined the relationship between BCL-2 gene family variants and endometrial cancer risk

among 1,028 patients and 1,922 age-matched community controls from Shanghai, China. We also investigated possible interactions between genetic variants and established risk factors (demographic, lifestyle and clinical). Individuals were genotyped for 86 tagging single nucleotide polymorphisms (SNPs) in the BCL2, BAX, BAD and BAK1 genes. RESULTS: Significant associations with endometrial cancer risk were found for 9 SNPs in the BCL2 gene (P trend<0.05 for all). For SNPs rs17759659 and rs7243091 (minor allele for both: G), the associations were independent. The odds ratio was 1.27 (95% CI: 1.04-1.53) for women with AG genotype for the SNP rs17759659 and 1.82 (95% CI: 1.21-2.73) for women with the GG genotype for the SNP rs7243091. No interaction between these two SNPs and established non-genetic risk factors of endometrial cancer was noticed. CONCLUSION: Genetic polymorphisms in the BCL2 gene may be associated with the risk of endometrial cancer in Chinese women.

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[898]

**TÍTULO / TITLE:** - Decreased FOXF2 mRNA Expression Indicates Early-Onset Metastasis and Poor Prognosis for Breast Cancer Patients with Histological Grade II Tumor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 19;8(4):e61591. doi: 10.1371/journal.pone.0061591. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061591](http://1371/journal.pone.0061591)

**AUTORES / AUTHORS:** - Kong PZ; Yang F; Li L; Li XQ; Feng YM

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China.

**RESUMEN / SUMMARY:** - The transcription factor, FOXF2, plays an important role in tissue development, extracellular matrix synthesis, and epithelial-mesenchymal interactions, implying that it may be associated with the metastatic capabilities of cancer cells. However, the relationship between FOXF2 expression and breast cancer progression, metastasis, and prognosis, remains to be elucidated. In this study, FOXF2 mRNA levels in 305 primary breast cancer tissues were examined using RT-QPCR. Results showed that FOXF2 mRNA levels in primary breast cancer were negatively associated with tumor progression, including tumor size, number of metastatic lymph nodes, and clinical stage. Patients with low FOXF2 mRNA levels had a high risk of relapse and metastasis within three years. Low FOXF2 mRNA levels could predict shorter disease-free survival for those patients with histological grade II and triple-negative breast cancer. Taken together, we conclude that decreased FOXF2 expression indicates the early-onset metastasis and poor prognosis for patients with histological grade II and triple-negative breast cancer.

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[899]

**TÍTULO / TITLE:** - Whole-Genome mRNA Expression Profiling Identifies Functional and Prognostic Signatures in Patients with Mesenchymal Glioblastoma Multiforme.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - CNS Neurosci Ther. 2013 May 11. doi: 10.1111/cns.12118.

●●Enlace al texto completo (gratis o de pago) [1111/cns.12118](#)

**AUTORES / AUTHORS:** - Bao ZS; Zhang CB; Wang HJ; Yan W; Liu YW; Li MY; Zhang W

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

**RESUMEN / SUMMARY:** - BACKGROUND: The Cancer Genome Atlas (TCGA) has divided patients with glioblastoma multiforme (GBM) into four subtypes based on mRNA expression microarray. The mesenchymal subtype, with a larger proportion, is considered a more lethal one. Clinical outcome prediction is required to better guide more personalized treatment for these patients. AIMS: The objective of this study was to identify a mRNA expression signature to improve outcome prediction for patients with mesenchymal GBM. RESULTS: For signature identification and validation, we downloaded mRNA expression microarray data from TCGA as training set and data from Rembrandt and GSE16011 as validation set. Cox regression and risk-score analysis were used to develop the 4 signatures, which were function and prognosis associated as revealed by Gene Ontology (GO) analysis and Gene Set Variation Analysis (GSVA). Patients who had high-risk scores according to the signatures had poor overall survival compared with patients who had low-risk scores. CONCLUSIONS: The signatures were identified as risk predictors that patients who had a high-risk score tended to have unfavorable outcome, demonstrating their potential for personalizing cancer management.

[900]

**TÍTULO / TITLE:** - Efficacy of exemestane in Korean patients with metastatic breast cancer after failure of nonsteroidal aromatase inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Breast Cancer. 2013 Mar;16(1):66-71. doi: 10.4048/jbc.2013.16.1.66. Epub 2013 Mar 31.

●●Enlace al texto completo (gratis o de pago) [4048/jbc.2013.16.1.66](#)

**AUTORES / AUTHORS:** - Lee JK; Im SA; Lee D; Kim JY; Lim Y; Lee E; Moon HG; Kim TY; Han SW; Oh DY; Lee SH; Han W; Kim DW; Kim TY; Noh DY

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea.

**RESUMEN / SUMMARY:** - PURPOSE: Exemestane has shown good efficacy and tolerability in postmenopausal women with hormone receptor-positive metastatic breast cancer. However, clinical outcomes in Korean patients have not yet been reported. METHODS: Data on 112 postmenopausal women with

metastatic breast cancer were obtained retrospectively. Clinicopathological characteristics and treatment history were extracted from medical records. All patients received 25 mg exemestane daily until objective disease progression. Progression-free survival (PFS) was the primary endpoint, and secondary endpoints were overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR=complete response+partial response+stable disease for 6 months). RESULTS: The median age of the subjects was 55 years (range, 28-76 years). Exemestane treatment resulted in a median PFS of 5.7 months (95% confidence interval [CI], 4.4-7.0 months) and median OS of 21.9 months (95% CI, 13.6-30.3 months). ORR was 6.4% and CBR was 46.4% for the 110 patients with evaluable lesions. Symptomatic visceral disease was independently associated with shorter PFS (hazard ratio, 3.611; 95% CI, 1.904-6.848;  $p < 0.001$ ), compared with bone-dominant disease in a multivariate analysis of PFS after adjusting for age, hormone receptor, human epidermal growth factor receptor 2, Ki-67 status, dominant metastasis site, and sensitivity to nonsteroidal aromatase inhibitor (AI) treatment. Sensitivity to previous nonsteroidal AI treatment was not associated with PFS, suggesting no cross-resistance between exemestane and nonsteroidal AIs. CONCLUSION: Exemestane was effective in postmenopausal Korean women with hormone receptor-positive metastatic breast cancer who failed previous nonsteroidal AI treatment.

[901]

**TÍTULO / TITLE:** - Thymoquinone induces apoptosis in oral cancer cells through p38beta inhibition.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Chin Med. 2013;41(3):683-96. doi: 10.1142/S0192415X1350047X.

●●Enlace al texto completo (gratis o de pago)

[1142/S0192415X1350047X](#)

**AUTORES / AUTHORS:** - Abdelfadil E; Cheng YH; Bau DT; Ting WJ; Chen LM; Hsu HH; Lin YM; Chen RJ; Tsai FJ; Tsai CH; Huang CY

**INSTITUCIÓN / INSTITUTION:** - Graduate Institute of Basic Medical Science, China Medical University, Taichung, Taiwan, Oral and Maxillofacial Department, Faculty of Dentistry, Department of Surgical Oncology, Oncology Center, Mansoura University, Egypt.

**RESUMEN / SUMMARY:** - Oral cancer is a common malignancy associated with high morbidity and mortality. While p38 MAPK is reported to be involved in different cellular activities such as proliferation and differentiation, reports rarely define the roles of the individual members of the p38 MAPK family in cancer. We used two unique cell lines developed by our lab representing chemically induced oral cancer cells (T28) and non-tumor cells (N28) obtained from tissues surrounding the induced cancer as a model to screen out whether p38 MAPK is involved in the malignant transformation processes. The results suggest an

association between p38beta not p38alpha and oral cancer development. Additionally, the anti-cancer activity of thymoquinone (TQ) was screened out and we found evidences suggesting that the anti-tumor activity of TQ may be attributed to the downregulation of p38beta MAPK.

[902]

**TÍTULO / TITLE:** - P38 MAP Kinase Mediates Apoptosis After Genipin Treatment in Non-Small-Cell Lung Cancer H1299 Cells via a Mitochondrial Apoptotic Cascade.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pharmacol Sci. 2013;121(4):272-81.

**AUTORES / AUTHORS:** - Yang X; Yao J; Luo Y; Han Y; Wang Z; Du L

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Bio-resources and Eco-environment of the Ministry of Education, College of Life Sciences, Sichuan University, China.

**RESUMEN / SUMMARY:** - Genipin, an active constituent of Gardenia fruit, has been reported to show an anti-tumor effect in several cancer cell systems. Here, we demonstrate how genipin exhibits a strong apoptotic cell death effect in human non-small-cell lung cancer H1299 cells. Genipin-mediated decrease in cell viability was observed through apoptosis as demonstrated by induction of a sub-G1 peak through flow cytometry, DNA fragmentation measured by TUNEL assay, and cleavage of poly ADP-ribose-polymerase. During genipin-induced apoptosis, the mitochondrial execution pathway was activated by caspase-9 and -3 activation as examined by a kinetic study, cytochrome c release, and a dose-dependent increase in Bax/Bcl-2 ratio. A search for the downstream pathway reveals that genipin-induced apoptosis was mediated by an increase in phosphorylated p38MAPK expression, which further activated downstream signaling by phosphorylating ATF-2. SB203580, a p38MAPK inhibitor, markedly blocked the formation of TUNEL-positive apoptotic cells in genipin-treated cells. Besides, the interference of p38MAPK inhibited Bax expression and cytochrome c release. Altogether, our observations imply that genipin causes increased levels of Bax in response to p38MAPK signaling, which results in the initiation of mitochondrial death cascade, and therefore it holds promise as a potential chemotherapeutic agent for the treatment of H1299 cells.

[903]

**TÍTULO / TITLE:** - Prognostic significance of postoperative serum carcinoembryonic antigen levels in patients with completely resected pathological-stage I non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cardiothorac Surg. 2013 Apr 22;8(1):106.

●●Enlace al texto completo (gratuito o de pago) [1186/1749-8090-8-106](#)

**AUTORES / AUTHORS:** - Kozu Y; Maniwa T; Takahashi S; Isaka M; Ohde Y; Nakajima T

**RESUMEN / SUMMARY:** - BACKGROUND: Until date, there are no clear recommendations for regular perioperative measurements of serum CEA levels for lung cancer in any guidelines. The purpose in the present study is to evaluate the prognostic significance of perioperative serum carcinoembryonic antigen (CEA) levels in patients with pathological-stage I non-small cell lung cancer (NSCLC). METHODS: We retrospectively reviewed 263 completely resected pathological-stage I NSCLC patients whose preoperative and postoperative serum CEA levels were measured. Patients were subdivided according to the perioperative change of CEA levels: continuously normal CEA levels (NN group), continuously high CEA levels (HH group), and high preoperative CEA levels that returned to normal levels post-operation (HN group). The clinicopathological factors and overall survival (OS) among these 3 groups were compared. Univariate and multivariate analyses of the correlation between clinicopathological factors and OS were performed. RESULTS: High preoperative CEA levels significantly correlated with men aged >70 years with smoking history, high serum CYFRA 21--1 levels, greater tumor diameter, presence of visceral pleural invasion (VPI), and moderate-to-poor differentiation. Five-year OS rates in the NN and HH groups were 95.5% and 59.3%, respectively. Four-year OS rate in the HN group was 85.5%. Multivariate analyses indicated tumor diameter of more than 30 mm, presence of VPI, and the HH group were independent unfavorable prognostic factors. CONCLUSIONS: A high postoperative CEA level was an independent unfavorable prognostic factor in pathological-stage I NSCLC patients. Patients with high postoperative CEA levels may benefit from adjuvant chemotherapy.

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[904]

**TÍTULO / TITLE:** - PI3K/AKT/mTOR Signaling is Involved in (-)-Epigallocatechin-3-Gallate-Induced Apoptosis of Human Pancreatic Carcinoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Chin Med. 2013;41(3):629-42. doi: 10.1142/S0192415X13500444.

●●Enlace al texto completo (gratis o de pago)

[1142/S0192415X13500444](#)

**AUTORES / AUTHORS:** - Liu S; Wang XJ; Liu Y; Cui YF

**INSTITUCIÓN / INSTITUTION:** - The 2<sup>nd</sup> Affiliated Hospital of Harbin Medical University, Harbin, China.

**RESUMEN / SUMMARY:** - PI3K/AKT/mTOR signaling promotes cell survival, proliferation and progression in cancer cells. Targeting this pathway may lead to the development of novel therapeutic approaches for human cancers. Here, we examined the effects of (-)-epigallocatechin-3-gallate (EGCG) on the PI3K/AKT/mTOR pathway in pancreatic cancer cells, and assessed its therapeutic potential. In this study, the proliferation and apoptosis of PANC-1

cells were examined by MTT assay and flow cytometry, respectively. The expression of genes and proteins involved in the PI3K/AKT/mTOR pathway were measured by RT-PCR and western blotting, respectively. Our results revealed that EGCG dramatically inhibited the proliferation of PANC-1 cells and induced apoptosis simultaneously. Furthermore, it upregulated PTEN mRNA and protein expression levels, as well as downregulating the expression of phospho-AKT and phospho-mTOR. In conclusion, these results suggest that EGCG can suppress proliferation and induce apoptosis of PANC-1 cells in a time- and dose-dependent manner; moreover, EGCG also can upregulate PTEN expression and downregulate the expression of pAKT and p-mTOR to modulate the PI3K/AKT/mTOR signaling pathway.

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[905]

**TÍTULO / TITLE:** - A248, a novel synthetic HDAC inhibitor, induces apoptosis through the inhibition of specificity protein 1 and its downstream proteins in human prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jul;8(1):195-200. doi: 10.3892/mmr.2013.1481. Epub 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1481](#)

**AUTORES / AUTHORS:** - Choi ES; Han G; Park SK; Lee K; Kim HJ; Cho SD; Kim HM

**INSTITUCIÓN / INSTITUTION:** - Department of Oral Pathology, School of Dentistry and Institute of Oral Bioscience, Brain Korea 21 Project, Chonbuk National University, Jeonju 561-756, Republic of Korea.

**RESUMEN / SUMMARY:** - Histone deacetylase (HDAC) inhibitors are emerging as potent anticancer agents due to their ability to induce apoptosis in various cancer cells, including prostate cancer cells. In the present study, we synthesized a novel HDAC inhibitor, A248, and investigated its apoptotic activity and molecular target in the DU145 and PC3 human prostate cancer cell lines. A248 inhibited the growth of DU145 and PC3 cells and induced apoptosis, as demonstrated by nuclear fragmentation and the accumulation of cells at subG1 phase of cell cycle. The treatment of DU145 and PC3 prostate cancer cells with A248 resulted in the downregulation of specificity protein 1 (Sp1) expression. Since the expression levels of survivin and Mcl-1 depend on Sp1, we also investigated the effects of A248 on survivin and Mcl-1 expression using western blot analysis and immunocytochemistry. The results showed that A248 markedly decreased the expression of survivin and Mcl-1. These data suggest that A248 has apoptotic activity in human prostate cancer cells and that Sp1 may be the molecular target of A248 treatment for inducing apoptosis in prostate cancer cells.

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[906]

**TÍTULO / TITLE:** - CA-125 cut-off value as a predictor for complete interval debulking surgery after neoadjuvant chemotherapy in patients with advanced ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gynecol Oncol. 2013 Apr;24(2):141-5. doi: 10.3802/jgo.2013.24.2.141. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [3802/jgo.2013.24.2.141](http://3802/jgo.2013.24.2.141)

**AUTORES / AUTHORS:** - Furukawa N; Sasaki Y; Shigemitsu A; Akasaka J; Kanayama S; Kawaguchi R; Kobayashi H

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Nara Medical University, Nara, Japan.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** In the present study, we evaluated changes in CA-125 cut-off values predictive of complete interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) using receiver operating characteristic (ROC) analysis. **METHODS:** This retrospective single-institution study included patients with International Federation of Gynecology and Obstetrics (FIGO) stage III epithelial ovarian cancer and a pre-NAC serum CA-125 level of greater than 40 U/mL who were treated with neoadjuvant platinum-based chemotherapy followed by IDS between 1994 and 2009. Logistic regression analysis was used to evaluate univariate and independent multivariate associations with the effect of clinical, pathological, and CA-125 parameters on complete IDS, and ROC analysis was used to determine potential cut-off values of CA-125 for prediction of the possibility of complete IDS. **RESULTS:** Seventy-five patients were identified. Complete IDS was achieved in 46 (61.3%) patients and non-complete IDS was observed 29 (38.7%). Median pre-NAC CA-125 level was 639 U/mL (range, 57 to 6,539 U/mL) in the complete IDS group and 1,427 U/mL (range, 45 to 10,989 U/mL) in the non-complete IDS group. Median pre-IDS CA-125 level was 15 U/mL (range, 2 to 60 U/mL) in the complete IDS group and 53 U/mL (range, 5 to 980 U/mL) in the non-complete IDS group ( $p < 0.001$ ). Multivariate analyses performed with complete IDS as the endpoint revealed only pre-IDS CA-125 as an independent predictor. The odds ratio of non-complete IDS was 10.861 when the pre-IDS CA-125 level was greater than 20 U/mL. **CONCLUSION:** The present data suggest that in the setting of IDS after platinum-based NAC for advanced ovarian cancer, a pre-IDS CA-125 level less than 20 U/mL is an independent predictor of complete IDS.

[907]

**TÍTULO / TITLE:** - Vitamin D receptor gene polymorphisms and prognosis of breast cancer among African-American and Hispanic women.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e57967. doi: 10.1371/journal.pone.0057967. Epub 2013 Mar 12.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0057967](https://doi.org/10.1371/journal.pone.0057967)

**AUTORES / AUTHORS:** - Mishra DK; Wu Y; Sarkissyan M; Sarkissyan S; Chen Z; Shang X; Ong M; Heber D; Koeffler HP; Vadgama JV

**INSTITUCIÓN / INSTITUTION:** - Division of Cancer Research and Training, Center to Eliminate Cancer Health Disparities, Department of Internal Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, California, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Vitamin D plays a role in cancer development and acts through the vitamin D receptor (VDR). Although African-Americans have the lowest levels of serum vitamin D, there is a dearth of information on VDR gene polymorphisms and breast cancer among African-Americans and Hispanics. This study examines whether VDR gene polymorphisms are associated with breast cancer in these cohorts. METHODS: Blood was collected from 232 breast cancer patients (Cases) and 349 non-cancer subjects (Controls). Genotyping for four polymorphic variants of VDR (FokI, BsmI, TaqI and ApaI) was performed using the PCR-RFLP method. RESULTS: An increased association of the VDR-FokI f allele with breast cancer was observed in African-Americans (OR = 1.9, p = 0.07). Furthermore, the FbTA, FbtA and fbtA haplotypes were associated with breast cancer among African-Americans (p<0.05). Latinas were more likely to have the VDR-ApaI alleles (Aa or aa) (p = 0.008). The VDR-ApaI aa genotype was significantly associated with poorly-differentiated breast tumors (p = 0.04) in combined Cases. Kaplan-Meier survival analysis showed decreased 5-year disease-free-survival (DFS) in breast cancer patients who had the VDR-FokI FF genotype (p<0.05). The Cox regression with multivariate analysis revealed the independent predictor value of the VDR-FokI polymorphism for DFS. The other three variants of VDR (BsmI, TaqI and ApaI) were not associated with disease outcome. CONCLUSIONS: VDR haplotypes are associated with breast cancer in African-Americans, but not in Hispanic/Latinas. The VDR-FokI FF genotype is linked with poor prognosis in African-American women with breast cancer.

[908]

**TÍTULO / TITLE:** - Breast Cancer Patients' Views on the Use of Genomic Testing to Guide Decisions about Their Postoperative Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Public Health Genomics. 2013;16(3):110-7. doi: 10.1159/000349920. Epub 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1159/000349920](https://doi.org/10.1159/000349920)

**AUTORES / AUTHORS:** - Seror V; Marino P; Bertucci F; Mancini J; Extra JM; Ferrero JM; Bachelot T; Viens P; Julian-Reynier C

**INSTITUCIÓN / INSTITUTION:** - INSERM, UMR 912 'Economics and Social Sciences Applied to Health and Analysis of Medical Information', Marseille, France.

**RESUMEN / SUMMARY:** - Background/Aims: Incorporating gene expression profiling into routine clinical practices is beginning to be recommended as part of breast cancer treatment. The aim of the present study was to investigate the decision-making involved in genomic testing from the perspective of patients enrolled in a genomics-based clinical trial of adjuvant chemotherapy. Methods: The prospective SA02 clinical trial was designed to assess the clinical benefits of a genomic test on axillary lymph node-positive (N+) early breast cancer patients. The patients enrolled in the SA02 trial were defined by 'good prognosis' genomic test results consistent with the delivery of postoperative anthracycline-based chemotherapy without taxane. The present companion study was presented by oncologists to 64 out of the 88 patients enrolled. Data were collected using self-administered questionnaires. Results: The response rate was 67% (questionnaires were returned 35 days on average after enrolment in the trial). Only 33% of the respondents accurately recalled or described their genomic test results. Although most N+ patients classically undergo anthracycline/taxane adjuvant chemotherapy, 23% of the present respondents did not recall participating in the clinical study involving chemotherapy without taxanes. Recall was mainly associated with higher risk perception of chemotherapy-related side effects and better understanding of test results. Among the respondents who recalled participating in the trial, 39% experienced decisional conflicts. Conclusions: Devoting greater efforts to explaining genomic test results to patients could be highly relevant in terms of the trade-off between the risk of unnecessary chemotherapy-related side effects and the loss of survival time possibly resulting from less aggressive treatment.

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[909]

**TÍTULO / TITLE:** - Suppression of Cellular Apoptosis Susceptibility (CSE1L) Inhibits Proliferation and Induces Apoptosis in Colorectal Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):1017-21.

**AUTORES / AUTHORS:** - Zhu JH; Hong DF; Song YM; Sun LF; Wang ZF; Wang JW

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery and Laparoscopic Center, Second Affiliated Hospital, Zhejiang University School of Medicine, 2Hangzhou, China E-mail : [jiangweiwangdr@163.com](mailto:jiangweiwangdr@163.com).

**RESUMEN / SUMMARY:** - The cellular apoptosis susceptibility (CSE1L) gene has been demonstrated to regulate multiple cellular mechanisms including the mitotic spindle check point as well as proliferation and apoptosis. However, the importance of CSE1L in human colon cancer is largely unknown. In the present study, we examined expression levels of CSE1L mRNA by semiquantitative RT-PCR. A lentivirus-mediated small interfering RNA (siRNA) was used to knock down CSE1L expression in the human colon cancer cell line RKO. Changes in CSE1L target gene expression were determined by RT-PCR. Cell proliferation was examined by a high content screening assay. In vitro tumorigenesis was

measured by colony-formation assay. Cell cycle distribution and apoptosis were detected by flow cytometric analysis. We found CSE1L mRNA to be expressed in human colon cancer cells. Using a lentivirus based RNAi approach, CSE1L expression was significantly inhibited in RKO cells, causing cell cycle arrest in the G2/M and S phases and a delay in cell proliferation, as well as induction of apoptosis and an inhibition of colony growth capacity. Collectively, the results suggest that silencing of CSE1L may be a potential therapeutic approach for colon cancer.

[910]

**TÍTULO / TITLE:** - Plasma uric acid and tumor volume are highly predictive of outcome in nasopharyngeal carcinoma patients receiving intensity modulated radiotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Radiat Oncol. 2013 May 15;8(1):121.

●●Enlace al texto completo (gratis o de pago) [1186/1748-717X-8-121](#)

**AUTORES / AUTHORS:** - Lin H; Lin HX; Ge N; Wang HZ; Sun R; Hu WH

**RESUMEN / SUMMARY:** - BACKGROUND: The combined predictive value of plasma uric acid and primary tumor volume in nasopharyngeal carcinoma (NPC) patients receiving intensity modulated radiation therapy (IMRT) has not yet been determined. METHODS: In this retrospective study, plasma uric acid level was measured after treatment in 130 histologically-proven NPC patients treated with IMRT. Tumor volume was calculated from treatment planning CT scans. Overall (OS), progression-free (PFS) and distant metastasis-free (DMFS) survival were compared using Kaplan-Meier analysis and the log rank test, and Cox multivariate and univariate regression models were created. RESULTS: Patients with a small tumor volume (<27 mL) had a significantly better DMFS, PFS and OS than patients with a large tumor volume. Patients with a high post-treatment plasma uric acid level (>301  $\mu\text{mol/L}$ ) had a better DMFS, PFS and OS than patients with a low post-treatment plasma uric acid level. Patients with a small tumor volume and high post-treatment plasma uric acid level had a favorable prognosis compared to patients with a large tumor volume and low post-treatment plasma uric acid level (7-year overall OS, 100% vs. 48.7%,  $P < 0.001$  and PFS, 100% vs. 69.5%,  $P < 0.001$ ). CONCLUSIONS: Post-treatment plasma uric acid level and pre-treatment tumor volume have predictive value for outcome in NPC patients receiving IMRT. NPC patients with a large tumor volume and low post-treatment plasma uric acid level may benefit from additional aggressive treatment after IMRT.

[911]

**TÍTULO / TITLE:** - beta-catenin Overexpression in the Nucleus Predicts Progress Disease and Unfavourable Survival in Colorectal Cancer: A Meta-Analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 24;8(5):e63854. doi: 10.1371/journal.pone.0063854. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063854](http://dx.doi.org/10.1371/journal.pone.0063854)

**AUTORES / AUTHORS:** - Chen Z; He X; Jia M; Liu Y; Qu D; Wu D; Wu P; Ni C; Zhang Z; Ye J; Xu J; Huang J

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China ; Cancer Institute (Key Laboratory of Cancer Prevention & Intervention, National Ministry of Education, Provincial Key Laboratory of Molecular Biology in Medical Sciences), Zhejiang University School of Medicine, Hangzhou, China.

**RESUMEN / SUMMARY:** - **BACKGROUND:** beta-catenin plays a key role in the progression of colorectal cancer (CRC). However, its prognostic significance for patients with CRC remains controversial. **METHODOLOGY:** Identical search strategies were used to search relevant literatures in the PubMed, Embase and Web of Science databases. The correlation between beta-catenin expression and clinicopathological features and prognosis was analyzed. **PRINCIPAL FINDINGS:** A total of 18 studies met the inclusion criteria, which comprised 3665 cases. Meta-analysis suggested that beta-catenin overexpression in the nucleus was significantly associated with disease free survival (DFS) (n = 541 in 3 studies; HR = 1.87, 95% CI: 1.28-2.71; Z = 3.26; P = 0.001) and overall survival (OS) for CRC patients (n = 2630 in 10 studies; HR = 1.55, 95% CI: 1.12-2.14; Z = 2.62; P = 0.009). However, there was no significant association between beta-catenin expression in the cytoplasm and OS (n = 1327 in 3 studies; HR = 1.04, 95% CI: 0.88-1.24, Z = 0.46, P = 0.643). The combined odds ratio (OR) of beta-catenin in the nucleus indicated that beta-catenin overexpression was associated with advanced stage CRC (n = 950 in 7 studies; OR = 0.71, 95% CI: 0.53-0.94; Z = 2.35; P = 0.019) and metastasis of CRC (n = 628 in 5 studies; OR = 0.49, 95% CI: 0.25-0.96, Z = 2.06, P = 0.039). beta-catenin overexpression in the nucleus had no correlation with the tumor site (colon or rectum), differentiation grade, lymph node status or depth of invasion. The pooled ORs were 1.09 (95% CI: 0.41-2.91, Z = 0.18, P = 0.856), 1.27(95% CI: 0.76-2.10, Z = 0.92, P = 0.357), 0.71(95% CI: 0.46-1.09, Z = 1.58, P = 0.115) and 0.82(95% CI: 0.4-1.68, Z = 0.53, P = 0.594). **CONCLUSIONS:** This study showed that beta-catenin overexpression in the nucleus, rather than in the cytoplasm, appeared to be associated with progress disease and a worse prognosis for CRC patients.

[912]

**TÍTULO / TITLE:** - EGFR-targeted granzyme B expressed in NK cells enhances natural cytotoxicity and mediates specific killing of tumor cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(4):e61267. doi: 10.1371/journal.pone.0061267. Epub 2013 Apr 3.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061267](https://doi.org/10.1371/journal.pone.0061267)

**AUTORES / AUTHORS:** - Oberoi P; Jabulowsky RA; Bahr-Mahmud H; Wels WS  
**INSTITUCIÓN / INSTITUTION:** - Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus, Frankfurt am Main, Germany.

**RESUMEN / SUMMARY:** - Natural killer (NK) cells are highly specialized effectors of the innate immune system that hold promise for adoptive cancer immunotherapy. Their cell killing activity is primarily mediated by the pro-apoptotic serine protease granzyme B (GrB), which enters target cells with the help of the pore-forming protein perforin. We investigated expression of a chimeric GrB fusion protein in NK cells as a means to augment their antitumoral activity. For selective targeting to tumor cells, we fused the epidermal growth factor receptor (EGFR) peptide ligand transforming growth factor alpha (TGFalpha) to human pre-pro-GrB. Established human NKL natural killer cells transduced with a lentiviral vector expressed this GrB-TGFalpha (GrB-T) molecule in amounts comparable to endogenous wildtype GrB. Activation of the genetically modified NK cells by cognate target cells resulted in the release of GrB-T together with endogenous granzymes and perforin, which augmented the effector cells' natural cytotoxicity against NK-sensitive tumor cells. Likewise, GrB-T was released into the extracellular space upon induction of degranulation with PMA and ionomycin. Secreted GrB-T fusion protein displayed specific binding to EGFR-overexpressing tumor cells, enzymatic activity, and selective target cell killing in the presence of an endosomolytic activity. Our data demonstrate that ectopic expression of a targeted GrB fusion protein in NK cells is feasible and can enhance antitumoral activity of the effector cells.

[913]

**TÍTULO / TITLE:** - Eligibility for bevacizumab as an independent prognostic factor for patients with advanced non-squamous non-small cell lung cancer: a retrospective cohort study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e59700. doi: 10.1371/journal.pone.0059700. Epub 2013 Mar 26.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0059700](https://doi.org/10.1371/journal.pone.0059700)

**AUTORES / AUTHORS:** - Takagi Y; Toriihara A; Nakahara Y; Yomota M; Okuma Y; Hosomi Y; Shibuya M; Okamura T

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan. [yakagi-tmd@umin.net](mailto:yakagi-tmd@umin.net)

**RESUMEN / SUMMARY:** - BACKGROUND: Bevacizumab requires some unique eligibility criteria, such as absence of hemoptysis and major blood vessel invasion by the tumor. The prognostic impact of these bevacizumab-specific criteria has not been evaluated. METHODS: Patients with stage IIIB/IV, non-

squamous non-small cell lung cancer who started chemotherapy before the approval of bevacizumab were reviewed. Patients with impaired organ function, poor performance status or untreated/symptomatic brain metastasis were excluded before the evaluation of bevacizumab eligibility. We compared overall survival and time to treatment failure among patients who were eligible (Group A) or ineligible (Group B) to receive bevacizumab. RESULTS: Among 283 patients with stage IIIB/IV non-squamous non-small cell lung cancer, eligibility for bevacizumab was evaluated in 154 patients. Fifty-seven patients were considered ineligible (Group B) based on one or more of a history of hemoptysis (n = 20), major blood vessel invasion (n = 43) and cardiovascular disease (n = 8). The remaining 97 patients were classified into Group A. Overall survival was significantly better in Group A (median, 14.6 months) than in Group B (median, 7.1 months; p<0.0001). Time to treatment failure was also significantly longer in Group A (median, 6.9 months) than in Group B (median, 3.0 months; p<0.0001). Adjusted hazard ratios of bevacizumab eligibility for overall survival and time to treatment failure were 0.48 and 0.38 (95% confidence intervals, 0.33-0.70 and 0.25-0.58), respectively. CONCLUSION: Eligibility for bevacizumab itself represents a powerful prognostic factor for patients with non-squamous non-small cell lung cancer. The proportion of patients who underwent first-line chemotherapy without disease progression or unacceptable toxicity can also be biased by bevacizumab eligibility. Selection bias can be large in clinical trials of bevacizumab, so findings from such trials should be interpreted with extreme caution.

[914]

**TÍTULO / TITLE:** - Comparison of acute toxicity and mortality after two different dosing regimens of high-dose interleukin-2 for patients with metastatic melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Target Oncol. 2013 Apr 23.

●●Enlace al texto completo (gratis o de pago) [1007/s11523-013-0276-](#)

[7](#)

**AUTORES / AUTHORS:** - Alwan LM; Grossmann K; Sageser D; Van Atta J; Agarwal N; Gilreath JA

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy Services, University of Washington Medical Center/Seattle Cancer Care Alliance, 825 Eastlake Ave. East, Seattle, WA, 98109, USA, [lmiares@uw.edu](mailto:lmiares@uw.edu).

**RESUMEN / SUMMARY:** - We compared acute toxicity, drug exposure, in-hospital mortality, and inpatient length of stay between two currently recommended dosing protocols (from the National Comprehensive Cancer Network Guidelines) of high-dose interleukin-2 (IL-2) treatment for patients with metastatic melanoma. Patients with metastatic melanoma who received high-dose IL-2 treatment between 2003 and 2010 were identified. Chemotherapy orders, electronic medical records, paper medical charts, and patient discharge

summaries were reviewed retrospectively. We identified 13 patients who had received 600,000 units/kilogram (kg)/dose and 15 patients who had received 720,000 units/kg/dose. Patients in the 720,000 units/kg/dose group had a higher rate of grade 3 and 4 bilirubin elevations (34 vs. 12 %), weight gain (any grade, 96 vs. 89 %), and thrombocytopenia (any grade, 75 vs. 65 %). Patients receiving the higher dose also experienced more dose-limiting neurotoxicity (45 vs. 23 %), large-volume diarrhea (15 vs. 0 %), and hepatotoxicity (7 vs. 0 %). There was no in-hospital mortality during treatment in either group. The average length of stay was similar between both groups (5 days, SD = 1 for both groups), and the median cumulative IL-2 exposure was similar between both groups for the first course (10.1 vs. 10.5 million units/kg) and for all courses (approximately 11-12 million units/kg). Both high-dose IL-2 protocols had comparable in-hospital mortality and cumulative IL-2 exposure. The 720,000 units/kg/dose dosing scheme did not shorten the length of stay but did lead to greater acute toxicity. Therefore, as a result, we recommend 600,000 units/kg/dose when deciding between the two regimens.

[915]

**TÍTULO / TITLE:** - Predictive value of Ki67 for adjuvant chemotherapy in node-negative, hormone receptor-positive breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Assoc Thai. 2013 Feb;96 Suppl 2:S60-6.

**AUTORES / AUTHORS:** - Sutepvarnon A; Warnnissorn M; Srimuninnimit V

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Ki67 labeling index (Ki67 LI) is a measure of tumor proliferation. In breast cancer, evidence supporting its prognostic value is clear and its predictive value for response to treatment finds some benefits. However studies of Ki67 LI as a predictive marker in early breast cancer are still limited worldwide and there is no data in Thailand. **OBJECTIVE:** To assess the predictive value of Ki67 expression for adjuvant chemotherapy in patients with node-negative, hormone receptor-positive breast cancer **MATERIAL AND METHOD:** The authors retrospectively evaluated 127 diagnosed early breast cancer with node-negative, hormone receptor-positive patients and receiving adjuvant systemic treatment at Siriraj hospital. Disease free survival (DFS) was compared with the log-rank test according to Ki67 LI and adjuvant systemic treatment (chemoendocrine therapy and endocrine therapy alone). **RESULTS:** At a median follow-up of 3.3 years. The 5-year DFS rate was 79% for patients with low Ki67 expression and 75% for patients with high Ki67 expression. Of the 127 patients, 56 (44.1%) received chemoendocrine therapy and 71 (55.9%) were treated with endocrine therapy alone. There was no different effect of DFS among those receiving adjuvant endocrine therapy alone and those receiving adjuvant chemoendocrine therapy depending on Ki67 expression. **CONCLUSION:** Among patients with node-

negative, hormone receptor-positive breast cancer, a high Ki67 LI had worse DFS trend than a low Ki67 LI but the Ki67 LI did not predict the efficacy of adjuvant chemotherapy.

[916]

**TÍTULO / TITLE:** - Prognostic and predictive significance of MYC and KRAS alterations in breast cancer from women treated with neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e60576. doi: 10.1371/journal.pone.0060576. Epub 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060576](#)

**AUTORES / AUTHORS:** - Pereira CB; Leal MF; de Souza CR; Montenegro RC; Rey JA; Carvalho AA; Assumpcao PP; Khayat AS; Pinto GR; Demachki S; de Arruda Cardoso Smith M; Burbano RR

**INSTITUCIÓN / INSTITUTION:** - Mastology Unit, Ophir Loyola Hospital, Belem, PA, Brazil.

**RESUMEN / SUMMARY:** - Breast cancer is a complex disease, with heterogeneous clinical evolution. Several analyses have been performed to identify the risk factors for breast cancer progression and the patients who respond best to a specific treatment. We aimed to evaluate whether the hormone receptor expression, HER2 and MYC genes and their protein status, and KRAS codon 12 mutations may be prognostic or predictive biomarkers of breast cancer. Protein, gene and mutation status were concomitantly evaluated in 116 breast tumors from women who underwent neoadjuvant chemotherapy with doxorubicin plus cyclophosphamide. We observed that MYC expression was associated with luminal B and HER2 overexpression phenotypes compared to luminal A ( $p < 0.05$ ). The presence of MYC duplication or polysomy 8, as well as KRAS mutation, were also associated with the HER2 overexpression subtype ( $p < 0.05$ ). MYC expression and MYC gain were more frequently observed in early-onset compared to late-onset tumors ( $p < 0.05$ ). KRAS mutation was a risk factor of grade 3 tumors ( $p < 0.05$ ). A multivariate logistic regression demonstrated that MYC amplification defined as MYC/nucleus ratio of  $\geq 2.5$  was a protective factor for chemotherapy resistance. On the other hand, age and grade 2 tumors were a risk factor. Additionally, luminal B, HER2 overexpression, and triple-negative tumors presented increased odds of being resistant to chemotherapy relative to luminal A tumors. Thus, breast tumors with KRAS codon 12 mutations seem to present a worse prognosis. Additionally, MYC amplification may help in the identification of tumors that are sensitive to doxorubicin plus cyclophosphamide treatment. If confirmed in a large set of samples, these markers may be useful for clinical stratification and prognosis.

[917]

**TÍTULO / TITLE:** - Activation of AMP-Activated Protein Kinase alpha and Extracellular Signal-Regulated Kinase Mediates CB-PIC-Induced Apoptosis in Hypoxic SW620 Colorectal Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med.

2013;2013:974313. doi: 10.1155/2013/974313. Epub 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago) [1155/2013/974313](#)

**AUTORES / AUTHORS:** - Cho SY; Lee HJ; Lee HJ; Jung DB; Kim H; Sohn EJ; Kim B; Jung JH; Kwon BM; Kim SH

**INSTITUCIÓN / INSTITUTION:** - College of Oriental Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea.

**RESUMEN / SUMMARY:** - Here, antitumor mechanism of cinnamaldehyde derivative CB-PIC was elucidated in human SW620 colon cancer cells. CB-PIC significantly exerted cytotoxicity, increased sub-G1 accumulation, and cleaved PARP with apoptotic features, while it enhanced the phosphorylation of AMPK alpha and ACC as well as activated the ERK in hypoxic SW620 cells.

Furthermore, CB-PIC suppressed the expression of HIF1 alpha, Akt, and mTOR and activated the AMPK phosphorylation in hypoxic SW620 cells. Conversely, silencing of AMPK alpha blocked PARP cleavage and ERK activation induced by CB-PIC, while ERK inhibitor PD 98059 attenuated the phosphorylation of AMPK alpha in hypoxic SW620 cells, implying cross-talk between ERK and AMPK alpha. Furthermore, cotreatment of CB-PIC and metformin enhanced the inhibition of HIF1 alpha and Akt/mTOR and the activation of AMPK alpha and pACC in hypoxic SW620 cells. In addition, CB-PIC suppressed the growth of SW620 cells inoculated in BALB/c athymic nude mice, and immunohistochemistry revealed that CB-PIC treatment attenuated the expression of Ki-67, CD34, and CAIX and increased the expression of pAMPK alpha in CB-PIC-treated group. Interestingly, CP-PIC showed better antitumor activity in SW620 colon cancer cells under hypoxia than under normoxia, since it may be applied to chemoresistance. Overall, our findings suggest that activation of AMPK alpha and ERK mediates CB-PIC-induced apoptosis in hypoxic SW620 colon cancer cells.

[918]

**TÍTULO / TITLE:** - Role of mTOR inhibition in preventing resistance and restoring sensitivity to hormone-targeted and HER2-targeted therapies in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Adv Hematol Oncol. 2013 Apr;11(4):217-24.

**AUTORES / AUTHORS:** - Mayer I

**INSTITUCIÓN / INSTITUTION:** - Vanderbilt University School of Medicine/Vanderbilt-Ingram Cancer Center, Nashville, TN 37232, USA.

**RESUMEN / SUMMARY:** - Even with hormone-targeted and human epidermal growth factor receptor 2 (HER2)-targeted anticancer agents, intrinsic resistance

or acquired resistance are common occurrences in estrogen receptor-positive and HER2-positive breast cancers, respectively. Potential mechanisms for resistance to targeted agents include steric inhibition imposed by other cellular elements, molecular changes in the target receptor, alterations in the regulation of downstream signaling components, compensatory cross-talk with other signaling pathways, and pharmacogenetic alterations in the host. Evidence suggests that both hormone receptor-positive tumors and HER2-overexpressing tumors use the phosphoinositide 3-kinase/Akt/ mammalian target of rapamycin (mTOR) pathway to escape control of antihormone and anti-HER2 therapies. The combination of mTOR inhibitors with hormone-targeted or HER2-targeted therapies appears to be a promising strategy for overcoming resistant disease and preventing the development of resistance.

[919]

**TÍTULO / TITLE:** - Acridone Derivative 8a Induces Oxidative Stress-Mediated Apoptosis in CCRF-CEM Leukemia Cells: Application of Metabolomics in Mechanistic Studies of Antitumor Agents.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 7;8(5):e63572. doi: 10.1371/journal.pone.0063572. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063572](http://1371/journal.pone.0063572)

**AUTORES / AUTHORS:** - Wang Y; Gao D; Chen Z; Li S; Gao C; Cao D; Liu F; Liu H; Jiang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, Tsinghua University, Beijing, China ; The Key Laboratory of Tumor Metabolomics at Shenzhen, Shenzhen, China.

**RESUMEN / SUMMARY:** - A new acridone derivative, 2-aminoacetamido-10-(3, 5-dimethoxy)-benzyl-9(10H)-acridone hydrochloride (named 8a) synthesized in our lab shows potent antitumor activity, but the mechanism of action remains unclear. Herein, we report the use of an UPLC/Q-TOF MS metabolomic approach to study the effects of three compounds with structures optimized step-by-step, 9(10H)-acridone (A), 10-(3,5-dimethoxy)benzyl-9(10H)-acridone (I), and 8a, on CCRF-CEM leukemia cells and to shed new light on the probable antitumor mechanism of 8a. Acquired data were processed by principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) to identify potential biomarkers. Comparing 8a-treated CCRF-CEM leukemia cells with vehicle control (DMSO), 23 distinct metabolites involved in five metabolic pathways were identified. Metabolites from glutathione (GSH) and glycerophospholipid metabolism were investigated in detail, and results showed that GSH level and the reduced/oxidized glutathione (GSH/GSSG) ratio were significantly decreased in 8a-treated cells, while L-cysteinyl-glycine (L-Cys-Gly) and glutamate were greatly increased. In glycerophospholipid metabolism, cell membrane components

phosphatidylcholines (PCs) were decreased in 8a-treated cells, while the oxidative products lysophosphatidylcholines (LPCs) were significantly increased. We further found that in 8a-treated cells, the reactive oxygen species (ROS) and lipid peroxidation product malondialdehyde (MDA) were notably increased, accompanied with decrease of mitochondrial transmembrane potential, release of cytochrome C and activation of caspase-3. Taken together our results suggest that the acridone derivative 8a induces oxidative stress-mediated apoptosis in CCRF-CEM leukemia cells. The UPLC/Q-TOF MS based metabolomic approach provides novel insights into the mechanistic studies of antitumor drugs from a point distinct from traditional biological investigations.

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[920]

**TÍTULO / TITLE:** - Variants in tamoxifen metabolizing genes: a case-control study of contralateral breast cancer risk in the WECARE study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Epidemiol Genet. 2013;4(1):35-48. Epub 2013 Mar 18.

**AUTORES / AUTHORS:** - Brooks JD; Teraoka SN; Malone KE; Haile RW; Bernstein L; Lynch CF; Mellekjaer L; Duggan DJ; Reiner AS; Concannon P; Schiermeyer K; Lewinger JP; Bernstein JL; Figueiredo JC

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center USA.

**RESUMEN / SUMMARY:** - Tamoxifen has been shown to greatly reduce risk of recurrence and contralateral breast cancer (CBC). Still, second primary contralateral breast cancer is the most common malignancy to follow a first primary breast cancer. Genetic variants in CYP2D6 and other drug-metabolizing enzymes that alter the metabolism of tamoxifen may be associated with CBC risk in women who receive the drug. This is the first study to investigate the impact of this variation on risk of CBC in women who receive tamoxifen. From the population-based Women's Environment Cancer and Radiation Epidemiology (WECARE) Study, we included 624 Caucasian women with CBC (cases) and 1,199 women with unilateral breast cancer (controls) with complete information on tumor characteristics and treatment. Conditional logistic regression was used to assess the risk of CBC associated with 112 single nucleotide polymorphisms (SNPs) in 8 genes involved in the metabolism of tamoxifen among tamoxifen users and non-users. After adjustment for multiple testing, no significant association was observed between any of the genotyped variants and CBC risk in either tamoxifen users or non-users. These results suggest that when using a tagSNP approach, common variants in selected genes involved in the metabolism of tamoxifen are not associated with risk of CBC among women treated with the drug.

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[921]

**TÍTULO / TITLE:** - A caspase-3 'death-switch' in colorectal cancer cells for induced and synchronous tumor apoptosis in vitro and in vivo facilitates the development of minimally invasive cell death biomarkers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 May 2;4:e613. doi: 10.1038/cddis.2013.137.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.137](http://1038/cddis.2013.137)

**AUTORES / AUTHORS:** - Simpson KL; Cawthorne C; Zhou C; Hodgkinson CL; Walker MJ; Trapani F; Kadirvel M; Brown G; Dawson MJ; Macfarlane M; Williams KJ; Whetton AD; Dive C

**INSTITUCIÓN / INSTITUTION:** - Clinical and Experimental Pharmacology Group, Paterson Institute for Cancer Research, University of Manchester and Manchester Cancer Research Centre, Wilmslow Road, Withington, Manchester, UK.

**RESUMEN / SUMMARY:** - Novel anticancer drugs targeting key apoptosis regulators have been developed and are undergoing clinical trials. Pharmacodynamic biomarkers to define the optimum dose of drug that provokes tumor apoptosis are in demand; acquisition of longitudinal tumor biopsies is a significant challenge and minimally invasive biomarkers are required. Considering this, we have developed and validated a preclinical 'death-switch' model for the discovery of secreted biomarkers of tumour apoptosis using in vitro proteomics and in vivo evaluation of the novel imaging probe [(18)F]ML-10 for non-invasive detection of apoptosis using positron emission tomography (PET). The 'death-switch' is a constitutively active mutant caspase-3 that is robustly induced by doxycycline to drive synchronous apoptosis in human colorectal cancer cells in vitro or grown as tumor xenografts. Death-switch induction caused caspase-dependent apoptosis between 3 and 24 hours in vitro and regression of 'death-switched' xenografts occurred within 24 h correlating with the percentage of apoptotic cells in tumor and levels of an established cell death biomarker (cleaved cytokeratin-18) in the blood. We sought to define secreted biomarkers of tumor apoptosis from cultured cells using Discovery Isobaric Tag proteomics, which may provide candidates to validate in blood. Early after caspase-3 activation, levels of normally secreted proteins were decreased (e.g. Gelsolin and Midkine) and proteins including CD44 and High Mobility Group protein B1 (HMGB1) that were released into cell culture media in vitro were also identified in the bloodstream of mice bearing death-switched tumors. We also exemplify the utility of the death-switch model for the validation of apoptotic imaging probes using [(18)F]ML-10, a PET tracer currently in clinical trials. Results showed increased tracer uptake of [(18)F]ML-10 in tumours undergoing apoptosis, compared with matched tumour controls imaged in the same animal. Overall, the death-switch model represents a robust and versatile tool for the discovery and validation of apoptosis biomarkers.

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[922]

**TÍTULO / TITLE:** - Homoharringtonine and SAHA synergistically enhance apoptosis in human acute myeloid leukemia cells through upregulation of TRAIL and death receptors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jun;7(6):1838-44. doi: 10.3892/mmr.2013.1440. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1440](#)

**AUTORES / AUTHORS:** - Cao H; Cheng Y; You L; Qian J; Qian W

**INSTITUCIÓN / INSTITUTION:** - Institute of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, P.R. China.

**RESUMEN / SUMMARY:** - Singleagent histone deacetylase (HDAC) inhibitors have exhibited marked antileukemic activity in preclinical and clinical studies and have undergone trials in combination with standard chemotherapeutics. However, the mechanisms of action of combination therapies are not completely understood. In the present study, a novel strategy for treatment of acute myeloid leukemia (AML) was identified, in which the chemotherapeutic agent, homoharringtonine (HHT), was combined with suberoylanilide hydroxamic acid (SAHA), a panHDAC inhibitor. A synergistic effect was observed when HHT was added to SAHA to induce apoptosis in Kasumi1 and THP1 leukemia cells. This combination was found to significantly enhance the activation of caspase8 and 9 compared with treatment with each drug separately. Notably, while SAHA induced upregulation of death receptor 4 (DR4) and DR5, HHT upregulated tumor necrosis factorrelated apoptosis-inducing ligand (TRAIL) expression in a dosedependent manner. In addition, the synergistic effect between HHT and SAHA was blocked partially using a specific antiTRAIL antibody. The combination therapy was also found to significantly inhibit the growth of leukemia xenografts in vivo with enhanced apoptosis. These results indicate that, by regulating the induction of TRAIL and activation of the TRAIL apoptotic pathway, it is possible to administer HHT at low concentrations in combination with SAHA as an effective therapeutic approach for the treatment of AML.

[923]

**TÍTULO / TITLE:** - Expression of MiR200a, miR93, Metastasis-related Gene RECK and MMP2/MMP9 in Human Cervical Carcinoma - Relationship with Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(3):2113-8.

**AUTORES / AUTHORS:** - Wang L; Wang Q; Li HL; Han LY

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Jilin University, Changchun, Jilin, China E-mail : [zanghu@163.com](mailto:zanghu@163.com).

**RESUMEN / SUMMARY:** - Aim and Background: Cervical cancer remains the third most common cancer in women globally after breast and colorectal cancer. Well-characterized biomarkers are necessary for early diagnosis and to predict metastatic progression and effective therapy. MiRNAs can regulate gene expression, cell growth, differentiation and apoptosis by targeting mRNAs for translational repression or degradation in tumor cells. The present study was conducted to assess expression of miR93, miR200a, RECK, MMP2, MMP9 in invasive cervical carcinoma, and analyze their clinical significance. Method: A total of 116 patients with invasive cervical carcinoma and 100 patients undergoing hysterectomy for benign lesions were retrospectively examined. Quantitative real-time PCR was performed to determine expression of miR93 and miR200a while RECK, MMP2, MMP9 and MVD were assessed by immunohistochemical staining. Results: Cervical carcinoma patients demonstrated up-regulation of miR-93, miR-200a, MMP2 and MMP9, with down-regulation of RECK as compared to benign lesion tissues. RECK was significantly inversely related to invasion and lymphatic metastasis. The 5-year survival rate for patients with strong RECK expression was significantly higher than that with weakly expressing tumors. Conclusion: MiR-93 and miR-200a are associated with metastasis and invasion of cervical carcinoma. Thus together with RECK they are potential prognostic markers for cervical carcinoma. RECK cooperating with MMP2, MMP9 expression is a significant prognostic factor correlated with long-term survival for patients with invasive cervical carcinoma.

[924]

**TÍTULO / TITLE:** - Efficacy and safety of lenalidomide in patients with myelodysplastic syndrome with chromosome 5q deletion.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ther Adv Hematol. 2012 Apr;3(2):105-16. doi: 10.1177/2040620711435659.

●●Enlace al texto completo (gratis o de pago)

[1177\\_2040620711435659](#) [pii]

●●Enlace al texto completo (gratis o de pago)

[1177/2040620711435659](#)

**AUTORES / AUTHORS:** - Duong VH; Komrokji RS; List AF

**RESUMEN / SUMMARY:** - Myelodysplastic syndrome (MDS) with del(5q) is a unique hematopoietic stem cell disease that typically follows an indolent course and demonstrates particular sensitivity to lenalidomide, a second-generation immunomodulatory agent. Early trials demonstrated rapid and durable responses leading to US Food and Drug Administration (FDA) approval in 2005. Definitive confirmatory evidence from a large phase III trial was recently published. Other recent advances include a better understanding of the pathogenesis of disease including haploinsufficiency of several candidate genes,

and elucidation of the lenalidomide-specific effect on two phosphatases ultimately leading to p53 degradation in the erythroid progenitors and cell cycle arrest in earlier myeloid progenitors. In this review, we describe the pathogenesis of MDS with del(5q), summarize the major clinical studies establishing the activity of lenalidomide in this population, discuss commonly encountered adverse events, and shed light on practical uses of this agent in the clinic.

[925]

**TÍTULO / TITLE:** - Blood neutrophil-lymphocyte ratio predicts survival for stages III-IV gastric cancer treated with neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg Oncol. 2013 May 24;11:112. doi: 10.1186/1477-7819-11-112.

●●Enlace al texto completo (gratis o de pago) [1186/1477-7819-11-112](#)

**AUTORES / AUTHORS:** - Jin H; Zhang G; Liu X; Liu X; Chen C; Yu H; Huang X; Zhang Q; Yu J

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, the First Affiliated Hospital, Medical College, Zhejiang University, No, 79, Qingchun Road, Hangzhou, Zhejiang Province 310003, China. [yujr0909@zju.edu.cn](mailto:yujr0909@zju.edu.cn).

**RESUMEN / SUMMARY:** - BACKGROUND: Accurate predictors of survival for patients with advanced gastric cancer treated with neoadjuvant chemotherapy are currently lacking. In this study, we aimed to evaluate the prognostic significance of the neutrophil-lymphocyte ratio (NLR) in patients with stage III-IV gastric cancer who received neoadjuvant chemotherapy. METHODS: We enrolled 46 patients in this study. The NLR was divided into two groups: high (>2.5) and low (<=2.5). Univariate analysis on progression-free survival (PFS) and overall survival(OS) was performed using the Kaplan-Meier and log-rank tests, and multivariate analysis was conducted using the Cox proportional hazards regression model. We analyzed whether chemotherapy normalized high NLR or not, and evaluated the prognostic significance of normalization on survival. RESULTS: The univariate analysis showed that PFS and OS were both worse for patients with high NLR than for those with low NLR before chemotherapy (median PFS 16 and 49 months, respectively, P = 0.012; median OS 21 and 52 months, P = 0.113). PFS and OS were also worse for patients with high NLR than for those with low NLR before surgery (median PFS 12 and 35 months, P = 0.019; median OS 21 and 52 months, P = 0.082). Multivariate analysis showed that both NLR before chemotherapy and surgery were independent prognostic factors of PFS. Neoadjuvant chemotherapy normalized high NLR in 11 of 24 patients, and these 11 patients had better median PFS and OS than the 13 patients who had high NLR both before chemotherapy and before surgery (PFS: 35.0 and 10.0 months, P = 0.003; OS: 60 and 16 months, P = 0.042). CONCLUSIONS: NLR may serve as a potential biomarker for

survival prognosis in patients with stage III-IV gastric cancer receiving neoadjuvant chemotherapy.

[926]

**TÍTULO / TITLE:** - Effects of poly (ADP-ribosyl) polymerase (PARP) inhibitor on cisplatin resistance & proliferation of the ovarian cancer C13 FNx01 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Indian J Med Res. 2013 Mar;137(3):527-32.

**AUTORES / AUTHORS:** - Zhang J; Kan Y; Tian Y; Wang Z; Zhang J

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics & Gynecology & Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China.

**RESUMEN / SUMMARY:** - Background & objectives: Drug resistance is the primary cause of failure in the treatment of cancers. It has been suggested that the enhancement of DNA repair capability may be responsible for the drug resistance of the tumour cells, and poly(ADP-ribosyl)ation plays an important role in DNA repair. This study investigated the effect of PARP inhibitor 3-aminobenzamide (3-AB) on the cisplatin resistance and proliferation of the cisplatin-resistant ovarian cancer C13 FNx01 cells in vitro. Methods: C13 FNx01 cells were treated with various concentrations of 3-AB in vitro. MTT assay was used to determine the effect of 3-AB on the cisplatin sensitivity and proliferation of cells. The expression levels of PARP-1 mRNA and protein in the C13 FNx01 cells were examined using reverse transcription-polymerase chain reaction (RT-PCR) and Western blot, and changes caused by 3-AB treatment were investigated. Immunofluorescence microscopy was used to detect the localization and expression of the PARP-1 proteins before and after treatment with 5 mmol/l 3-AB. Results: The inhibitory ratio and the cisplatin sensitivity of C13 FNx01 cells significantly increased with the increase of the concentration of 3-AB ( $P < 0.05$ ). The RT-PCR analysis revealed that the expression of PARP-1 mRNA was decreased when platinum (Pt) and 3-AB were combined. The expression levels of PARP-1 protein were decreased by 23.15 +/- 2.53, 59.11 +/- 2.23 and 73.24 +/- 3.88 per cent, respectively, in C13 FNx01 cells with the increase of the concentration of 3-AB ( $P < 0.05$ ). The immunofluorescence microscopy results indicated that the expression level of PARP-1 protein was significantly decreased after treatment with 3-AB ( $P < 0.05$ ). Interpretation & conclusions: 3-AB inhibited the proliferation activity of C13 FNx01 cells, and increased the cellular sensitivity to cisplatin. Our findings show that the PARP inhibitor 3-AB can downregulate the expression of PARP-1 at transcriptional and translational levels in C13 FNx01 cells.

[927]

**TÍTULO / TITLE:** - Targeting mechanisms of resistance to anti-EGF receptor therapy in KRAS wild-type colorectal cancer: the path to more personalized medicine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 Apr;9(4):551-60. doi: 10.2217/fon.12.204.

●●Enlace al texto completo (gratis o de pago) [2217/fon.12.204](#)

**AUTORES / AUTHORS:** - Fakhri M

**INSTITUCIÓN / INSTITUTION:** - City of Hope, 1500 E Duarte Road, Building 51, Room 127, Duarte, CA 91010, USA. [mfakhri@coh.org](mailto:mfakhri@coh.org)

**RESUMEN / SUMMARY:** - The targeting of EGF receptors (EGFRs) in metastatic colorectal cancer has improved the outcome of patients with KRAS wild-type tumors. However, these improvements have been modest and do not translate across all patients with KRAS wild-type tumors. Better understanding of the EGFR pathway has led to the exploration of variable novel potential biomarkers of resistance and response to anti-EGFR therapy. This manuscript will focus on recently identified mechanisms of resistance to anti-EGFR therapy in KRAS wild-type colorectal cancer. Subsequently, an assessment will be presented on how the current understanding of some of these mechanisms of resistance has led, and will lead, to novel therapeutic opportunities in the management of colorectal cancer.

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[928]

**TÍTULO / TITLE:** - The synergistic apoptotic interaction of Indole-3-Carbinol and Genistein with TRAIL on endometrial cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Korean Med Sci. 2013 Apr;28(4):527-33. doi: 10.3346/jkms.2013.28.4.527. Epub 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago)

[3346/jkms.2013.28.4.527](#)

**AUTORES / AUTHORS:** - Parajuli B; Shin SJ; Kwon SH; Cha SD; Lee HG; Bae I; Cho CH

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Keimyung University, School of Medicine, Daegu, Korea.

**RESUMEN / SUMMARY:** - Induction of apoptosis in target cells is a key mechanism by which chemotherapy promotes cell killing. The purpose of this study was to determine whether Indole-3-Carbinol (I3C) and Genistein in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induce apoptosis in endometrial cancer cell (Ishikawa) and to assess apoptotic mechanism. The MTT assay and flow cytometry were performed to determine cell viability and cell cycle. The induction of apoptosis was measured by caspase-3 activity test, DNA fragmentation assay, annexin V binding assay and western blot analysis. There was no effect in cell growth inhibition and cell cycle progression alone or in two-combination. However, the treatment of I3C and Genistein followed by TRAIL showed significant cell death and marked increase in sub-G1 arrest. Three-combination treatment revealed elevated expression of DR4, DR5 and cleaved forms of caspase-3, caspase-8, PARP.

The Flip was found down regulated. Moreover, increase in caspase-3 activity and DNA fragmentation indicated the induction of apoptosis. The results indicate that I3C and Genistein with TRAIL synergistically induced apoptosis via death receptor dependent pathway. Our findings might provide a new insight into the development of novel combination therapies against endometrial cancer.

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[929]

**TÍTULO / TITLE:** - Involvement of melastatin type transient receptor potential 7 channels in ginsenoside Rd-induced apoptosis in gastric and breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Ginseng Res. 2013 Apr;37(2):201-9. doi: 10.5142/jgr.2013.37.201.

●●Enlace al texto completo (gratis o de pago) [5142/jgr.2013.37.201](#)

**AUTORES / AUTHORS:** - Kim BJ

**INSTITUCIÓN / INSTITUTION:** - Division of Longevity and Biofunctional Medicine, School of Korean Medicine, Pusan National University, Yangsan 626-870, Korea.

**RESUMEN / SUMMARY:** - Ginsenoside, one of the active ingredients of Panax ginseng, has a variety of physiologic and pharmacologic effects. The purpose of this study was to explore the effects of ginsenoside Rd (G-Rd) on melastatin type transient receptor potential 7 (TRPM7) channels with respect to the proliferation and survival of AGS and MCF-7 cells (a gastric and a breast cancer cell line, respectively). AGS and MCF-7 cells were treated with different concentrations of G-Rd, and caspase-3 activities, mitochondrial depolarizations, and sub-G1 fractions were analyzed to determine if cell death occurred by apoptosis. In addition, human embryonic kidney (HEK) 293 cells overexpressing TRPM7 channels were used to confirm the role of TRPM7 channels. G-Rd inhibited the proliferation and survival of AGS and MCF-7 cells and enhanced caspase-3 activity, mitochondrial depolarization, and sub-G1 populations. In addition, G-Rd inhibited TRPM7-like currents in AGS and MCF-7 cells and in TRPM7 channel overexpressing HEK 293 cells, as determined by whole cell voltage-clamp recordings. Furthermore, TRPM7 overexpression in HEK 293 cells promoted G-Rd induced cell death. These findings suggest that G-Rd inhibits the proliferation and survival of gastric and breast cancer cells by inhibiting TRPM7 channel activity.

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[930]

**TÍTULO / TITLE:** - Correction to Sulforaphane Potentiates the Efficacy of Imatinib against Chronic Leukemia Cancer Stem Cells through Enhanced Abrogation of Wnt/beta-Catenin Function.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Agric Food Chem. 2013 May 20.

●●Enlace al texto completo (gratis o de pago) [1021/jf402029d](http://1021/jf402029d)

**AUTORES / AUTHORS:** - Lin LC; Yeh CT; Kuo CC; Lee CM; Yen GC; Wang LS; Wu CH; Yang WC; Wu AT

[931]

**TÍTULO / TITLE:** - Chimeric antigen receptor containing ICOS signaling domain mediates specific and efficient antitumor effect of T cells against EGFRvIII expressing glioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hematol Oncol. 2013 May 9;6:33. doi: 10.1186/1756-8722-6-33.

●●Enlace al texto completo (gratis o de pago) [1186/1756-8722-6-33](http://1186/1756-8722-6-33)

**AUTORES / AUTHORS:** - Shen CJ; Yang YX; Han EQ; Cao N; Wang YF; Wang Y; Zhao YY; Zhao LM; Cui J; Gupta P; Wong AJ; Han SY

**INSTITUCIÓN / INSTITUTION:** - Translational Research Center, Zhengzhou University People's Hospital, #7 Weiwu Road, Zhengzhou, Henan 450003, China. [shuangyinhan@zzu.edu.cn](mailto:shuangyinhan@zzu.edu.cn).

**RESUMEN / SUMMARY:** - BACKGROUND: Adoptive transfer of chimeric antigen receptor (CAR)-modified T cells appears to be a promising immunotherapeutic strategy. CAR combines the specificity of antibody and cytotoxicity of cytotoxic T lymphocytes, enhancing T cells' ability to specifically target antigens and to effectively kill cancer cells. Recent efforts have been made to integrate the costimulatory signals in the CAR to improve the antitumor efficacy. Epidermal growth factor receptor variant III (EGFRvIII) is an attractive therapeutic target as it frequently expresses in glioma and many other types of cancers. Our current study aimed to investigate the specific and efficient antitumor effect of T cells modified with CAR containing inducible costimulator (ICOS) signaling domain. METHODS: A second generation of EGFRvIII/CAR was generated and it contained the EGFRvIII single chain variable fragment, ICOS signaling domain and CD3zeta chain. Lentiviral EGFRvIII/CAR was prepared and human CD3+ T cells were infected by lentivirus encoding EGFRvIII/CAR. The expression of EGFRvIII/CAR on CD3+ T cells was confirmed by flow cytometry and Western blot. The functions of EGFRvIII/CAR+ T cells were evaluated using in vitro and in vivo methods including cytotoxicity assay, cytokine release assay and xenograft tumor mouse model. RESULTS: Chimeric EGFRvIIIscFv-ICOS-CD3zeta (EGFRvIII/CAR) was constructed and lentiviral EGFRvIII/CAR were made to titer of 10<sup>6</sup> TU/ml. The transduction efficiency of lentiviral EGFRvIII/CAR on T cells reached around 70% and expression of EGFRvIII/CAR protein was verified by immunoblotting as a band of about 57 kDa. Four hour <sup>51</sup>Cr release assays demonstrated specific and efficient cytotoxicity of EGFRvIII/CAR+ T cells against EGFRvIII expressing U87 cells. A robust increase in the IFN-gamma secretion was detected in the co-culture

supernatant of the EGFRvIII/CAR+ T cells and the EGFRvIII expressing U87 cells. Intravenous and intratumor injection of EGFRvIII/CAR+ T cells inhibited the in vivo growth of the EGFRvIII expressing glioma cells. CONCLUSIONS: Our study demonstrates that the EGFRvIII/CAR-modified T cells can destroy glioma cells efficiently in an EGFRvIII specific manner and release IFN-gamma in an antigen dependent manner. The specific recognition and effective killing activity of the EGFRvIII-directed T cells with ICOS signaling domain lays a foundation for us to employ such approach in future cancer treatment.

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[932]

**TÍTULO / TITLE:** - Golden Berry-Derived 4beta-hydroxywithanolide E for Selectively Killing Oral Cancer Cells by Generating ROS, DNA Damage, and Apoptotic Pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 21;8(5):e64739. doi: 10.1371/journal.pone.0064739. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064739](#)

**AUTORES / AUTHORS:** - Chiu CC; Haung JW; Chang FR; Huang KJ; Huang HM; Huang HW; Chou CK; Wu YC; Chang HW

**INSTITUCIÓN / INSTITUTION:** - Department of Biotechnology, Kaohsiung Medical University, Kaohsiung, Taiwan.

**RESUMEN / SUMMARY:** - BACKGROUND: Most chemotherapeutic drugs for killing cancer cells are highly cytotoxic in normal cells, which limits their clinical applications. Therefore, a continuing challenge is identifying a drug that is hypersensitive to cancer cells but has minimal deleterious effects on healthy cells. The aims of this study were to evaluate the potential of 4beta-hydroxywithanolide (4betaHWE) for selectively killing cancer cells and to elucidate its related mechanisms. METHODOLOGY AND PRINCIPAL FINDINGS: Changes in survival, oxidative stress, DNA damage, and apoptosis signaling were compared between 4betaHWE-treated oral cancer (Ca9-22) and normal fibroblast (HGF-1) cells. At 24 h and 48 h, the numbers of Ca9-22 cells were substantially decreased, but the numbers of HGF-1 cells were only slightly decreased. Additionally, the IC50 values for 4betaHWE in the Ca9-22 cells were 3.6 and 1.9 microg/ml at 24 and 48 h, respectively. Time-dependent abnormal increases in ROS and dose-responsive mitochondrial depolarization can be exploited by using 4betaHWE in chemotherapies for selectively killing cancer cells. Dose-dependent DNA damage measured by comet-nuclear extract assay and flow cytometry-based gamma-H2AX/propidium iodide (PI) analysis showed relatively severer damage in the Ca9-22 cells. At both low and high concentrations, 4betaHWE preferably perturbed the cell cycle in Ca9-22 cells by increasing the subG1 population and arrest of G1 or G2/M. Selective induction of apoptosis in Ca9-22 cells was further confirmed by Annexin V/PI assay, by preferential expression of phosphorylated ataxia-telangiectasia- and Rad3-

related protein (p-ATR), and by cleavage of caspase 9, caspase 3, and poly ADP-ribose polymerase (PARP). CONCLUSIONSSIGNIFICANCE: Together, the findings of this study, particularly the improved understanding of the selective killing mechanisms of 4betaHWE, can be used to improve efficiency in killing oral cancer cells during chemoprevention and therapy.

[933]

**TÍTULO / TITLE:** - Two Cases of Myeloproliferative Neoplasm with a Concurrent JAK2 (V617F) Mutation and BCR/ABL Translocation without Chronic Myelogenous Leukemia Phenotype Acquisition during Hydroxyurea Treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Lab Med. 2013 May;33(3):229-32. doi: 10.3343/alm.2013.33.3.229. Epub 2013 Apr 17.

●●Enlace al texto completo (gratis o de pago) [3343/alm.2013.33.3.229](#)

**AUTORES / AUTHORS:** - Park SH; Chi HS; Cho YU; Jang S; Park CJ; Kim DY; Lee JH; Lee KH

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, University of Ulsan, College of Medicine and Asan Medical Center, Seoul, Korea.

[934]

**TÍTULO / TITLE:** - Systematic antibody generation and validation via tissue microarray technology leading to identification of a novel protein prognostic panel in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Apr 2;13:175. doi: 10.1186/1471-2407-13-175.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-175](#)

**AUTORES / AUTHORS:** - O Leary PC; Penny SA; Dolan RT; Kelly CM; Madden SF; Rexhepaj E; Brennan DJ; McCann AH; Ponten F; Uhlen M; Zagozdzon R; Duffy MJ; Kell MR; Jirstrom K; Gallagher WM

**INSTITUCIÓN / INSTITUTION:** - UCD School of Biomolecular and Biomedical Science, UCD Conway Institute of Biomolecular and Biomedical Science, University College Dublin, Dublin 4, Ireland. [william.gallagher@ucd.ie](mailto:william.gallagher@ucd.ie).

**RESUMEN / SUMMARY:** - BACKGROUND: Although omic-based discovery approaches can provide powerful tools for biomarker identification, several reservations have been raised regarding the clinical applicability of gene expression studies, such as their prohibitive cost. However, the limited availability of antibodies is a key barrier to the development of a lower cost alternative, namely a discrete collection of immunohistochemistry (IHC)-based biomarkers. The aim of this study was to use a systematic approach to generate and screen affinity-purified, mono-specific antibodies targeting progression-related biomarkers, with a view towards developing a clinically applicable IHC-based prognostic biomarker panel for breast cancer. METHODS: We examined both in-house and publicly available breast cancer DNA microarray datasets

relating to invasion and metastasis, thus identifying a cohort of candidate progression-associated biomarkers. Of these, 18 antibodies were released for extended analysis. Validated antibodies were screened against a tissue microarray (TMA) constructed from a cohort of consecutive breast cancer cases (n = 512) to test the immunohistochemical surrogate signature. RESULTS: Antibody screening revealed 3 candidate prognostic markers: the cell cycle regulator, Anillin (ANLN); the mitogen-activated protein kinase, PDZ-Binding Kinase (PBK); and the estrogen response gene, PDZ-Domain Containing 1 (PDZK1). Increased expression of ANLN and PBK was associated with poor prognosis, whilst increased expression of PDZK1 was associated with good prognosis. A 3-marker signature comprised of high PBK, high ANLN and low PDZK1 expression was associated with decreased recurrence-free survival ( $p < 0.001$ ) and breast cancer-specific survival (BCSS) ( $p < 0.001$ ). This novel signature was associated with high tumour grade ( $p < 0.001$ ), positive nodal status ( $p = 0.029$ ), ER-negativity ( $p = 0.006$ ), Her2-positivity ( $p = 0.036$ ) and high Ki67 status ( $p < 0.001$ ). However, multivariate Cox regression demonstrated that the signature was not a significant predictor of BCSS (HR = 6.38; 95% CI = 0.79-51.26,  $p = 0.082$ ). CONCLUSIONS: We have developed a comprehensive biomarker pathway that extends from discovery through to validation on a TMA platform. This proof-of-concept study has resulted in the identification of a novel 3-protein prognostic panel. Additional biochemical markers, interrogated using this high-throughput platform, may further augment the prognostic accuracy of this panel to a point that may allow implementation into routine clinical practice.

[935]

**TÍTULO / TITLE:** - The clinical and prognostic implications of pluripotent stem cell gene expression in hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1155-1162. Epub 2013 Jan 23.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1151](#)

**AUTORES / AUTHORS:** - Yin X; Li YW; Jin JJ; Zhou Y; Ren ZG; Qiu SJ; Zhang BH

**INSTITUCIÓN / INSTITUTION:** - Liver Cancer Institute and Zhongshan Hospital, Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, Shanghai 200032, P.R. China.

**RESUMEN / SUMMARY:** - Recently, growing evidence has demonstrated that aberrant expression of pluripotent stem cell-related genes may confer primitive and aggressive traits and be associated with unfavorable clinical outcomes in certain solid cancers. However, the role of pluripotent stem cell gene expression in hepatocellular carcinoma (HCC) remains unexplored. We evaluated the expression of the pluripotent stem cell genes Oct4, Sox2 and Klf4, as well as that of the c-Myc, Nanog and Lin28 genes in HCC samples and corresponding adjacent non-tumor liver samples obtained from 57 patients using quantitative

real-time reverse transcription-PCR (qRT-PCR). The results revealed that six pluripotent stem cell gene expression levels were upregulated in the tumor tissues compared with the corresponding adjacent non-tumor liver tissues. In HCC tissues, aberrant expression of Sox2 and Lin28 was associated with a large tumor size ( $P=0.02$  and  $P=0.03$ , respectively), while increased expression levels of c-Myc ( $P=0.01$ ) were correlated with vascular invasion. Moreover, high Klf4 expression levels were associated with aggressive tumor behaviors in terms of vascular invasion ( $P=0.02$ ) and poor tumor differentiation ( $P=0.03$ ). Survival analysis revealed that Klf4 expression was independently associated with overall survival [OS; hazard ratio (HR), 8.61; 95% confidential interval (CI), 2.7-27.5;  $P<0.001$ ] and recurrence-free survival (RFS; HR, 3.96; 95% CI, 1.3-11.6;  $P=0.01$ ). In conclusion, pluripotent stem cell genes are associated with HCC progression and a poor prognosis. The development of therapeutic strategies, including adjuvant therapy, that take cancer stem cell (CSC)-related markers into consideration is likely to be a key factor in further improvements of the prognosis of HCC patients undergoing curative liver resection.

[936]

**TÍTULO / TITLE:** - Influence of serum and albumin on the in vitro anandamide cytotoxicity toward C6 glioma cells assessed by the MTT cell viability assay: implications for the methodology of the MTT tests.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Folia Neuropathol. 2013;51(1):44-50.

**AUTORES / AUTHORS:** - Bilmin K; Kopczynska B; Grieb P

**INSTITUCIÓN / INSTITUTION:** - Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland.

**RESUMEN / SUMMARY:** - Anandamide (AEA), an endogenous ligand of cannabinoid CB1 and CB2 receptors, which also binds transient receptor potential vanilloid type 1 receptor (TRPV1), has been shown to display substantial selective cytotoxicity toward some cancer cell lines in vitro, although the relevant data are not consistent. In the present study, we employed the MTT test to assess short-term cytotoxicity of AEA on C6 rat glioma cell culture. When anandamide was administered to the culture medium with foetal bovine serum (FBS), no cytotoxic effect was observed following 24 h exposure of the glioma cells to micromolar concentrations of AEA. However, if no serum was present in the medium, micro-to-submicromolar concentrations of AEA induced dose-dependent cytotoxicity clearly detectable after 24 h. Control experiments made it possible to exclude significant interference of serum with the MTT test per se. Bovine serum albumin mimicked the effect of FBS. We conclude that the apparent inhibition of short-term cytotoxicity of AEA toward C6 rat glioma cells in vitro is caused by binding AEA to serum proteins such as albumin. Taking into account that blood serum or albumin is practically always present in cell

culture media, we discuss implications of binding substances to serum proteins for methodology and interpretation of in vitro cytotoxicity testing.

[937]

**TÍTULO / TITLE:** - Absolute lymphocyte count predicts response to rituximab-containing salvage treatment for relapsed/refractory B-cell non-Hodgkin's lymphoma with prior rituximab exposure.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Chin Med Assoc. 2013 Apr;76(4):195-200. doi: 10.1016/j.jcma.2012.12.003. Epub 2013 Jan 23.

●●Enlace al texto completo (gratis o de pago) [1016/j.jcma.2012.12.003](#)

**AUTORES / AUTHORS:** - Hung MH; Yu YB; Hsiao LT; Hong YC; Liu JH; Gau JP; Chiou TJ; Chen PM; Tzeng CH; Liu CY

**INSTITUCIÓN / INSTITUTION:** - Division of Haematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC.

**RESUMEN / SUMMARY:** - BACKGROUND: Rituximab-containing salvage chemotherapy has shown promising efficacy in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma (NHL). The aim of this study was to examine the efficacy of rituximab-containing treatment in patients with B-cell NHL who developed relapsed or refractory disease after prior rituximab use and to explore the predictive factors of response using this approach. METHODS: Patients with relapsed/refractory B-cell NHL who received rituximab-containing salvage treatment after failing first-line rituximab-combining chemotherapy were enrolled in this retrospective study. The characteristics of the patients were collected and analyzed. Logistic regression analysis was used for determining predictive factors of response to rituximab-containing salvage treatment. RESULTS: A total of 68 patients were enrolled in this study and the overall response rate to rituximab-containing salvage treatment was 61.7%. The median event-free survival and overall survival with rituximab-containing salvage treatment was 11.3 and 21.73 months, respectively. Results of a multivariate analysis showed high absolute lymphocyte count at the time of rituximab-containing salvage treatment [(ALC-R), ALC-R  $\geq$  1000/UL,  $p = 0.003$ ], which was the only independent factor predicting response to rituximab-containing salvage treatment. CONCLUSION: Our study results show that for patients with relapsed/refractory B-cell NHL, rituximab-containing salvage treatment is feasible and generally tolerable. A high ALC-R value was significantly associated with a better response to this treatment.

[938]

**TÍTULO / TITLE:** - Inhibition of Growth and Induction of Differentiation of SMMC-7721 Human Hepatocellular Carcinoma Cells by Oncostatin M.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):747-52.

**AUTORES / AUTHORS:** - Kong N; Zhang X; Wang H; Mu X; Han H; Yan W

**INSTITUCIÓN / INSTITUTION:** - Department of Regenerative Medicine, College of Pharmacy, Jilin University, Changchun, China E-mail : [wq\\_yan2008@163.com](mailto:wq_yan2008@163.com).

**RESUMEN / SUMMARY:** - Oncostatin M (OSM) is a multifunctional cellular regulator acting on a wide variety of cells, which has potential roles in the regulation of gene activation, cell survival, proliferation and differentiation. Previous studies have shown that OSM can induce morphological and/or functional differentiation and maturation of many tumor cells. However, the action of OSM on the induction of differentiation of human hepatocellular carcinoma (HCC) has not been reported. Here, we investigated the effects of different concentrations of OSM on human HCC cell line SMMC-7721 growth, proliferation, cell cycling, apoptosis and differentiation in vitro. Cell growth was determined via MTT assay, proliferation by cell cycle analysis, apoptosis by flow cytometry, morphology by transmission electronic microscopy, and cell function by detection of biochemical markers. Our results demonstrated that OSM strongly inhibited the growth of SMMC-7721 cells in a dose-dependent manner, associated with decreased clonogenicity. Cell cycle analysis revealed a decreased proportion of cells in S phase, with arrest at G0/G1. The apoptosis rate was increased after OSM treatment compared to the control. These changes were associated with striking changes in cellular morphology, toward a more mature hepatic phenotype, accompanied by significant reduction of the expression of AFP and specific activity of gamma-GT, with remarkable increase in secretion of albumin and ALP activity. Taken together, our findings indicate that OSM could induce the differentiation and reduce cell viability of SMMC-7721 cells, suggesting that differentiation therapy with OSM offers the opportunity for therapeutic intervention in HCC.

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[939]

**TÍTULO / TITLE:** - Polymorphisms in arachidonic acid metabolism-related genes and the risk and prognosis of colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Fam Cancer. 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s10689-013-9659-](http://1007/s10689-013-9659-2)

[2](#)

**AUTORES / AUTHORS:** - Li S; Zhao X; Wu Z; Li Y; Zhu L; Cui B; Dong X; Tian S; Hu F; Zhao Y

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology, Public Health College, Harbin Medical University, 157, Baojian Street, Nangang District, Harbin, Heilongjiang Province, People's Republic of China.

**RESUMEN / SUMMARY:** - Cyclooxygenase-2 (COX-2), 12-lipoxygenase (12-LOX) and phospholipaseA2 (PLA2) played important roles in the modulation of

apoptosis, angiogenesis, carcinogenesis and invasion of colorectal cancer (CRC). The polymorphisms in COX-2, 12-LOX and PLA2 may affect their roles. Therefore, we investigated if COX-2 -1195G > A, 12-LOX 261Arg > Gln and PLA2 c.349 + 191A > G polymorphisms were associated with risk and prognosis of CRC as well as possible interactions with the environmental factors on the risk of CRC in Northeast of China. A case-control study with 451 cases and 631 controls were carried out, a cohort with 386 patients were followed up. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Compared with the 261Arg/Arg genotype, 12-LOX 261Arg/Gln genotype and 261Arg/Gln + Gln/Gln genotypes reduced the risk of rectal cancer by 33 % (adjusted OR = 0.67, 95 % CI 0.47-0.97, p = 0.03) and 32 % (adjusted OR = 0.68, 95 % CI 0.49-0.96, p = 0.03), respectively. The adjusted HR for the association between 12-LOX 261Gln/Gln genotype and overall survival in patients with CRC was 1.68 (95 % CI 1.06-2.68, p = 0.03). There was also evidence of an interaction between the PLA2 c.349 + 191 A > G genotypes and the overnight food consumption (adjusted ORi = 1.92, 95 % CI 1.14-3.25, P interaction = 0.01). These observations indicate that 12-LOX 261Arg > Gln polymorphism may affect risk of rectal cancer, and it may be a potential predictive marker for prognosis of CRC.

[940]

**TÍTULO / TITLE:** - Cisplatin downregulates BCL2L12, a novel apoptosis-related gene, in glioblastoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - In Vitro Cell Dev Biol Anim. 2013 May 25.

●●Enlace al texto completo (gratis o de pago) [1007/s11626-013-9622-](#)

[4](#)

**AUTORES / AUTHORS:** - Taghavi MS; Akbarzadeh A; Mahdian R; Azadmanesh K; Javadi G

**INSTITUCIÓN / INSTITUTION:** - Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran, [ms.taghavi@srbiau.ac.ir](mailto:ms.taghavi@srbiau.ac.ir).

**RESUMEN / SUMMARY:** - Glioblastoma progression is mainly characterized by intense apoptosis resistance and marked necrosis. Over-expression of BCL2L12, a novel member of Bcl-2 family has been shown in primary glioblastoma. BCL2L12 blocks effective caspase-3/7 maturation and inhibits p53 tumor suppressor, deriving resistance toward apoptosis and inducing extensive cell necrosis. Cisplatin is a major chemotherapeutic agent which has a broad range of anti-neoplastic activities including apoptosis induction. To investigate the effect of cisplatin on the expression of BCL2L12 in glioblastoma cells, two glioblastoma cell lines were treated with different concentrations of cisplatin for 48 h. The cell viability and IC50 was determined using MTT assay. Then, the two glioblastoma cell lines were treated with 48 h IC50 concentration of cisplatin for 24, 48, and 72 h. Apoptosis induction was analyzed by

fluorescence microscopy and flow cytometry. Gene expression study was performed on BCL2L12 and TBP as target and internal control genes, respectively. The quantitative real-time polymerase chain reaction results showed that BCL2L12 gene expression was significantly ( $p = 0.001$ ) downregulated in the presence of cisplatin. In conclusion, cisplatin treatment induced a time-dependent apoptosis in glioblastoma cells, at least partially via downregulation of BCL2L12 gene expression.

[941]

**TÍTULO / TITLE:** - Erratum to: Bortezomib represses HIF-1alpha protein expression and nuclear accumulation by inhibiting both PI3K/Akt/TOR and MAPK pathways in prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Mol Med (Berl). 2013 Jun;91(6):771-3. doi: 10.1007/s00109-013-1030-4.

●●Enlace al texto completo (gratis o de pago) [1007/s00109-013-1030-4](#)

**AUTORES / AUTHORS:** - Befani CD; Vlachostergios PJ; Hatzidaki E; Patrikidou A; Bonanou S; Simos G; Papandreou CN; Liakos P

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Biochemistry, Faculty of Medicine, University of Thessaly, Biopolis, 41110, Larissa, Greece.

[942]

**TÍTULO / TITLE:** - Azacitidine in the management of patients with myelodysplastic syndromes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ther Adv Hematol. 2012 Dec;3(6):355-73. doi: 10.1177/2040620712464882.

●●Enlace al texto completo (gratis o de pago) [1177\\_2040620712464882](#) [pii]

●●Enlace al texto completo (gratis o de pago) [1177/2040620712464882](#)

**AUTORES / AUTHORS:** - Khan C; Pathe N; Fazal S; Lister J; Rossetti JM

**INSTITUCIÓN / INSTITUTION:** - Western Pennsylvania Cancer Institute, The Western Pennsylvania Hospital, Pittsburgh, PA, USA.

**RESUMEN / SUMMARY:** - Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis and potential transformation to acute myeloid leukemia (AML). For decades, the mainstay of treatment for MDS was supportive care, including transfusion of blood products and growth factors. Further understanding of disease biology led to the discovery of a high prevalence of hypermethylation of tumor suppressor genes in high-risk MDS and secondary leukemias. Hence, the role of irreversible DNA

methytransferase inhibitors such as azacitidine was investigated with promising outcomes in the treatment of MDS. Azacitidine was initially approved in the USA by the Food and Drug Administration (FDA) in 2004 for the treatment of all subtypes of MDS and was granted expanded approval in 2009 to reflect new overall survival data demonstrated in the AZA-001 study of patients with higher-risk MDS. Azacitidine has demonstrated significant and clinically meaningful prolongation of survival in higher-risk patients with MDS and has changed the natural history of these disorders. The agent maintains a relatively safe toxicity profile, even in older patients. The role of azacitidine has been explored in the treatment of AML and chronic myelomonocytic leukemia and has also been studied in the peritransplant setting. Azacitidine has been combined with other novel agents such as lenalidomide, histone deacetylase inhibitors and growth factors in the hope of achieving improved outcomes. Currently, both intravenous and subcutaneous forms of azacitidine are approved for use in the USA with the oral form being granted fast track status by the FDA.

[943]

**TÍTULO / TITLE:** - Interferon Stimulated Gene - ISG15 is a Potential Diagnostic Biomarker in Oral Squamous Cell Carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):1147-50.

**AUTORES / AUTHORS:** - Laljee RP; Muddaiah S; Salagundi B; Cariappa PM; Indra AS; Sanjay V; Ramanathan A

**INSTITUCIÓN / INSTITUTION:** - Department of Prosthodontics and Implantology, Coorg Institute of Dental Sciences, Coorg, Karnataka, India E-mail :

[drarvindram@yahoo.co.in](mailto:drarvindram@yahoo.co.in).

**RESUMEN / SUMMARY:** - Background: Cancer diagnostic biomarkers have a wide range of applications that include early detection of oral precancerous lesions and oral squamous cell carcinomas, and assessing the metastatic status of lesions. The interferon stimulated ISG15 gene encodes an ubiquitin-like protein, which conjugates to stabilize activation status of associated proteins. Hence a deregulated expression of ISG15 may promote carcinogenesis. Indeed overexpression of ISG15 has been observed in several cancers and hence it has been proposed as a strong candidate cancer diagnostic biomarker. Given the emerging relationship between malignant transformation and ISG15, we sought to examine the expression pattern of this gene in tumor biopsies of oral squamous cell carcinoma (OSCC) tissues collected from Indian patients. Materials and Methods: Total RNA isolated from thirty oral squamous cell carcinoma tissue biopsy samples were subjected to semi-quantitative RT-PCR with ISG15 specific primers to elucidate the expression level. Results: Of the thirty oral squamous cell carcinomas that were analyzed, ISG15 expression was found in twenty four samples (80%). Twelve samples expressed low level of ISG15, six of them expressed moderately, while the rest of them expressed very high level of ISG15. Conclusions: To the best of our knowledge, the results

show for the first time an overexpression of ISG15 in up to 80% of oral squamous cell carcinoma tissues collected from Indian patients. Hence ISG15 may be explored for the possibility of use as a high confidence diagnostic biomarker in oral cancers.

[944]

**TÍTULO / TITLE:** - Identification and validation of a new set of five genes for prediction of risk in early breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Sci. 2013 May 6;14(5):9686-702. doi: 10.3390/ijms14059686.

●●Enlace al texto completo (gratis o de pago) [3390/ijms14059686](#)

**AUTORES / AUTHORS:** - Mustacchi G; Sormani MP; Bruzzi P; Gennari A; Zanconati F; Bonifacio D; Monzoni A; Morandi L

**INSTITUCIÓN / INSTITUTION:** - Cancer Centre, ASS1 University of Trieste, Trieste 34012, Italy. [l.morandi@ausl.bo.it](mailto:l.morandi@ausl.bo.it).

**RESUMEN / SUMMARY:** - Molecular tests predicting the outcome of breast cancer patients based on gene expression levels can be used to assist in making treatment decisions after consideration of conventional markers. In this study we identified a subset of 20 mRNA differentially regulated in breast cancer analyzing several publicly available array gene expression data using R/Bioconductor package. Using RTqPCR we evaluate 261 consecutive invasive breast cancer cases not selected for age, adjuvant treatment, nodal and estrogen receptor status from paraffin embedded sections. The biological samples dataset was split into a training (137 cases) and a validation set (124 cases). The gene signature was developed on the training set and a multivariate stepwise Cox analysis selected five genes independently associated with DFS: FGF18 (HR = 1.13, p = 0.05), BCL2 (HR = 0.57, p = 0.001), PRC1 (HR = 1.51, p = 0.001), MMP9 (HR = 1.11, p = 0.08), SERF1a (HR = 0.83, p = 0.007). These five genes were combined into a linear score (signature) weighted according to the coefficients of the Cox model, as:  $0.125FGF18 - 0.560BCL2 + 0.409PRC1 + 0.104MMP9 - 0.188SERF1A$  (HR = 2.7, 95% CI = 1.9-4.0, p < 0.001). The signature was then evaluated on the validation set assessing the discrimination ability by a Kaplan Meier analysis, using the same cut offs classifying patients at low, intermediate or high risk of disease relapse as defined on the training set (p < 0.001). Our signature, after a further clinical validation, could be proposed as prognostic signature for disease free survival in breast cancer patients where the indication for adjuvant chemotherapy added to endocrine treatment is uncertain.

[945]

**TÍTULO / TITLE:** - In vitro and in vivo effects of geranylgeranyltransferase I inhibitor P61A6 on non-small cell lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Apr 22;13:198. doi: 10.1186/1471-2407-13-198.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-198](#)

**AUTORES / AUTHORS:** - Zimonjic DB; Chan LN; Tripathi V; Lu J; Kwon O; Popescu NC; Lowy DR; Tamanoi F

**INSTITUCIÓN / INSTITUTION:** - Department of Microbio,, Immunol, & Molec, Genet,, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA. [fuyut@microbio.ucla.edu](mailto:fuyut@microbio.ucla.edu).

**RESUMEN / SUMMARY:** - BACKGROUND: Lung cancer is the leading cause of cancer-related mortality. Therapies against non-small cell lung cancer (NSCLC) are particularly needed, as this type of cancer is relatively insensitive to chemotherapy and radiation therapy. We recently identified GGTI compounds that are designed to block geranylgeranylation and membrane association of signaling proteins including the Rho family G-proteins. One of the GGTIs is P61A6 which inhibits proliferation of human cancer cells, causes cell cycle effects with G1 accumulation and exhibits tumor-suppressing effects with human pancreatic cancer xenografts. In this paper, we investigated effects of P61A6 on non-small cell lung cancer (NSCLC) cells in vitro and in vivo. METHODS: Three non-small cell lung cancer cell lines were used to test the ability of P61A6 to inhibit cell proliferation. Further characterization involved analyses of geranylgeranylation, membrane association and activation of RhoA, and anchorage-dependent and -independent growth, as well as cell cycle effects and examination of cell cycle regulators. We also generated stable cells expressing RhoA-F, which bypasses the geranylgeranylation requirement of wild type RhoA, and examined whether the proliferation inhibition by P61A6 is suppressed in these cells. Tumor xenografts of NSCLC cells growing in nude mice were also used to test P61A6's tumor-suppressing ability. RESULTS: P61A6 was shown to inhibit proliferation of NSCLC lines H358, H23 and H1507. Detailed analysis of P61A6 effects on H358 cells showed that P61A6 inhibited geranylgeranylation, membrane association of RhoA and caused G1 accumulation associated with decreased cyclin D1/2. The effects of P61A6 to inhibit proliferation could mainly be ascribed to RhoA, as expression of the RhoA-F geranylgeranylation bypass mutant rendered the cells resistant to inhibition by P61A6. We also found that P61A6 treatment of H358 tumor xenografts growing in nude mice reduced their growth as well as the membrane association of RhoA in the tumors. CONCLUSION: Thus, P61A6 inhibits proliferation of NSCLC cells and causes G1 accumulation associated with decreased cyclin D1/2. The result with the RhoA-F mutant suggests that the effect of P61A6 to inhibit proliferation is mainly through the inhibition of RhoA. P61A6 also shows efficacy to inhibit growth of xenograft tumor.

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[946]

**TÍTULO / TITLE:** - The Src-family kinase inhibitor PP2 rescues inducible differentiation events in emergent retinoic acid-resistant myeloblastic leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e58621. doi: 10.1371/journal.pone.0058621. Epub 2013 Mar 15.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0058621](#)

**AUTORES / AUTHORS:** - Jensen HA; Styskal LE; Tasseff R; Bunaciu RP; Congleton J; Varner JD; Yen A

**INSTITUCIÓN / INSTITUTION:** - School of Chemical and Biomolecular Engineering, Cornell University, Ithaca, New York, USA.

**RESUMEN / SUMMARY:** - Retinoic acid is an embryonic morphogen and dietary factor that demonstrates chemotherapeutic efficacy in inducing maturation in leukemia cells. Using HL60 model human myeloid leukemia cells, where all-trans retinoic acid (RA) induces granulocytic differentiation, we developed two emergent RA-resistant HL60 cell lines which are characterized by loss of RA-inducible G1/G0 arrest, CD11b expression, inducible oxidative metabolism and p47(phox) expression. However, RA-treated RA-resistant HL60 continue to exhibit sustained MEK/ERK activation, and one of the two sequentially emergent resistant lines retains RA-inducible CD38 expression. Other signaling events that define the wild-type (WT) response are compromised, including c-Raf phosphorylation and increased expression of c-Cbl, Vav1, and the Src-family kinases (SFKs) Lyn and Fgr. As shown previously in WT HL60 cells, we found that the SFK inhibitor PP2 significantly increases G1/G0 cell cycle arrest, CD38 and CD11b expression, c-Raf phosphorylation and expression of the aforementioned regulators in RA-resistant HL60. The resistant cells were potentially incapable of developing inducible oxidative metabolism. These results motivate the concept that RA resistance can occur in steps, wherein growth arrest and other differentiation events may be recovered in both emergent lines. Investigating the mechanistic anomalies in resistant cell lines is of therapeutic significance and helps to mechanistically understand the response to retinoic acid's biological effects in WT HL60 cells.

[947]

**TÍTULO / TITLE:** - Progesterone Enhances Calcitriol Antitumor Activity by Upregulating Vitamin D Receptor Expression and Promoting Apoptosis in Endometrial Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Prev Res (Phila). 2013 May 16.

●●Enlace al texto completo (gratis o de pago) [1158/1940-6207.CAPR-12-0493](#)

**AUTORES / AUTHORS:** - Lee LR; Teng PN; Nguyen H; Hood BL; Kavandi L; Wang G; Turbov J; Thaete LG; Hamilton CA; Maxwell G; Rodriguez GC; Conrads TP; Syed V

**INSTITUCIÓN / INSTITUTION:** - 1Obstetrics and Gynecology, Uniformed Services University of the Health Sciences.

**RESUMEN / SUMMARY:** - Human studies suggest that progesterone and calcitriol may prove beneficial in preventing or inhibiting oncogenesis, but the underlying mechanism is not fully understood. The current study investigates the effects of progesterone, calcitriol and their combination on immortalized human endometrial epithelial cells and endometrial cancer cells and identifies their targets of action. Combination treatment with both agents enhanced vitamin D receptor expression and inhibited cell proliferation through caspase-3 activation and induction of G0/G1 cell cycle arrest with associated down-regulation of cyclins D1 and D3 and p27 induction. We used mass spectrometry-based proteomics to measure protein abundance differences between calcitriol-, progesterone-, or combination-exposed endometrial cells. A total of 117 proteins showed differential expression amongst these three treatments. Four proteins were then selected for validation studies: histone H1.4 (HIST1H1E), histidine triad nucleotide-binding protein 2 (HINT2), interferon-induced, double-stranded RNA-activated protein kinase (EIF2AK2), and Bcl-2-associated X protein (BAX). Abundance levels of selected candidates were low in endometrial cancer cell lines versus the immortalized endometrial epithelial cell line. All four proteins displayed elevated expression in cancer cells upon exposure to calcitriol, progesterone or the combination. Further BAX analysis through gain or loss of function experiments revealed that upregulation of BAX decreased cell proliferation by changing the BAX:BCL-2 ratio. Knock down of BAX attenuated progesterone- and calcitriol-induced cell growth inhibition. Our results showed that progesterone and calcitriol up-regulate the expression of BAX along with other apoptosis-related proteins, which induce inhibition of endometrial cancer cell growth by apoptosis and cell cycle arrest.

[948]

**TÍTULO / TITLE:** - In vitro and in vivo efficacy of doxorubicin loaded biodegradable semi-interpenetrating hydrogel implants of poly (acrylic acid)/gelatin for post surgical tumor treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Mater. 2013 May 29;8(4):045004.

●●Enlace al texto completo (gratis o de pago) [1088/1748-6041/8/4/045004](#)

**AUTORES / AUTHORS:** - Jaiswal M; Naz F; Dinda AK; Koul V

**INSTITUCIÓN / INSTITUTION:** - Centre for Biomedical Engineering, Indian Institute of Technology, New Delhi-110016, India. Department of Pathology, All India Institute of Medical Sciences, New Delhi-110029, India.

**RESUMEN / SUMMARY:** - The paper describes the preparation and evaluation of doxorubicin loaded semi-interpenetrating polymeric hydrogel network of polyacrylic acid (PAC) and gelatin (G). Post surgical antitumor efficacy and biodistribution of doxorubicin from the implanted degradable hydrogels was investigated on Ehrlich's ascites tumor model using albino mice. Polycaprolactone diacrylate (PCL-DAr) was employed as a crosslinking agent for PAC chains whereas G was kept free. The effect of crosslinking concentration on various physico-chemical properties such as thermal behavior, swelling, degradation behavior, drug release and polymer-polymer interactions was investigated by various physico-chemical tools. Semi-interpenetrating polymeric networks (IPNs) with 0.2 mol% crosslinking concentration showed degradation within 20 days in phosphate buffer (pH 6.5). To determine the in vivo anticancer efficacy, placebo and drug laden cylindrical implants (65 +/- 5 microg/implant of 10 mg) were implanted in tumor cavity post tumor excision. After predetermined time intervals (day 7, 11, 14, 20 and 25), drug biodistribution was assessed in tumor, tumor periphery, residual hydrogel and all vital organs i.e. liver, spleen, kidney, heart, lung and blood (spectrofluorimetrically). The drug distribution study showed the concentration of drug in the tumor, tumor periphery and residual hydrogel decreased with increasing time; on the 7<sup>th</sup> day, drug concentration was highest while, on the 25<sup>th</sup> day, it was negligible; however, insignificant quantities of the drug was found in vital organs. Histological examination revealed no sign of tumor recurrence until the 25<sup>th</sup> day with 100% necrosis and slight inflammation in treated the group. In vivo results established that these biodegradable implants can be utilized as post surgical therapy for solid tumors.

[949]

**TÍTULO / TITLE:** - Effect of neoadjuvant chemotherapy on stromal CD10 antigens in breast cancer - A preliminary study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Indian J Cancer. 2013 Jan-Mar;50(1):46-51. doi: 10.4103/0019-509X.112299.

●●Enlace al texto completo (gratis o de pago) [4103/0019-509X.112299](#)

**AUTORES / AUTHORS:** - Thomas S; Babu RJ; Agarwal K; Puri V; Jain M; Andley M; Tudu SK

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Lady Hardinge Medical College, Shaheed Bhagat Singh Marg, New Delhi, India.

**RESUMEN / SUMMARY:** - Introduction: CD10 is a zinc-dependent peptidase (metalloproteinase). Stromal CD10 expression in breast cancer correlates with poor prognosis, oestrogen receptor negativity and higher grade. CD10 may be a potential target of new cancer therapies as it is involved in cleavage of doxorubicin. Aim: To evaluate the effect of neo-adjuvant anthracycline-based chemotherapy on status of stromal CD10 antigens in breast cancer. Materials and Methods: Patients with invasive breast cancer scheduled for anthracycline-

based neo-adjuvant chemotherapy were included in the study. Tumor stromal CD10 expression was estimated before and after 3 cycles of chemotherapy, and change in its status was correlated with clinical response to chemotherapy. Results: 16 out of the 29 patients had strong CD10 expression; in these 16 patients, 14 (87.5%) were hormone receptor negative, and 14 (87.5%) had HER-2/neu overexpression. Stromal CD10 expression remained same in 13 out of 29 cases (44.83%) after chemotherapy. There was a change in CD10 expression in the remaining 16 cases (55.17%); in 13 cases (44.83%) it decreased from its pre-chemotherapy status, while its expression increased in 3 cases (10.34%). In cases of complete and partial clinical response, there was no increase in CD10 expression. Where CD10 expression had increased after chemotherapy, there was either a minor response or no response to chemotherapy. In 13 cases where CD10 expression had decreased, 12 cases had a clinical response to chemotherapy. Conclusions: Strong CD10 expression correlates with hormone receptor negativity and HER-2/neu overexpression. Stromal CD10 expression in breast cancer is not static and changes with neo-adjuvant anthracycline-based chemotherapy. A stable or decrease in CD10 expression correlates with complete or partial clinical response, while an increase in CD10 expression appears to correlate with poor clinical response. A larger series is required to determine the clinical significance of these changes. As stromal CD10 expression and its change with chemotherapy may have a prognostic significance, they should be documented in breast cancer patients before and after chemotherapy.

[950]

**TÍTULO / TITLE:** - Inhibition of the receptor tyrosine kinase ROR1 by anti-ROR1 monoclonal antibodies and siRNA induced apoptosis of melanoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 8;8(4):e61167. doi: 10.1371/journal.pone.0061167. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061167](#)

**AUTORES / AUTHORS:** - Hojjat-Farsangi M; Ghaemimanesh F; Daneshmanesh AH; Bayat AA; Mahmoudian J; Jeddi-Tehrani M; Rabbani H; Mellstedt H

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology-Pathology, Immune and Gene therapy Lab, Cancer Center Karolinska, Karolinska University Hospital Solna and Karolinska Institute, Stockholm, Sweden.

**RESUMEN / SUMMARY:** - The receptor tyrosine kinase (RTK) ROR1 is overexpressed and of importance for the survival of various malignancies, including lung adenocarcinoma, breast cancer and chronic lymphocytic leukemia (CLL). There is limited information however on ROR1 in melanoma. In the present study we analysed in seven melanoma cell lines ROR1 expression and phosphorylation as well as the effects of anti-ROR1 monoclonal antibodies

(mAbs) and ROR1 suppressing siRNA on cell survival. ROR1 was overexpressed at the protein level to a varying degree and phosphorylated at tyrosine and serine residues. Three of our four self-produced anti-ROR1 mAbs (clones 3H9, 5F1 and 1A8) induced a significant direct apoptosis of the ESTDAB049, ESTDAB112, DFW and A375 cell lines as well as cell death in complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). The ESTDAB081 and 094 cell lines respectively were resistant to direct apoptosis of the four anti-ROR1 mAbs alone but not in CDC or ADCC. ROR1 siRNA transfection induced downregulation of ROR1 expression both at mRNA and protein levels proceeded by apoptosis of the melanoma cells (ESTDAB049, ESTDAB112, DFW and A375) including ESTDAB081, which was resistant to the direct apoptotic effect of the mAbs. The results indicate that ROR1 may play a role in the survival of melanoma cells. The surface expression of ROR1 on melanoma cells may support the notion that ROR1 might be a suitable target for mAb therapy.

[951]

**TÍTULO / TITLE:** - Clinical significance of apoptosis-associated speck-like protein containing a caspase recruitment domain in oral squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Jun;115(6):799-809. doi: 10.1016/j.oooo.2013.03.013.

●●Enlace al texto completo (gratis o de pago) [1016/j.oooo.2013.03.013](http://1016/j.oooo.2013.03.013)

**AUTORES / AUTHORS:** - Shimane T; Kobayashi H; Takeoka M; Kitazawa M; Matsumura T; Hida S; Xiao T; Koike T; Taniguchi S; Kurita H

**INSTITUCIÓN / INSTITUTION:** - Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Asahi, Matsumoto, Japan. Electronic address: [shimane@shinshu-u.ac.jp](mailto:shimane@shinshu-u.ac.jp).

**RESUMEN / SUMMARY:** - OBJECTIVES: To assess apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) expression in oral squamous cell carcinoma (OSCC) and analyze its clinical and pathological significance. STUDY DESIGN: ASC expression was studied using immunohistochemistry in 119 OSCCs patients. The relationships between ASC expression and clinical and pathological parameters were statistically analyzed. In addition, the relationships between ASC expression and cell differentiation [IVL (involcrin) expression] and apoptosis (TUNEL [TdT-mediated dUTP nick end labeling] positive cell number) were investigated. RESULTS: ASC expression showed significant correlations with parameters including clinical tumor stage, mode of invasion, and histological differentiation, and had a significant impact on survival of OSCC. The distribution of ASC correlated well with that of IVL. ASC expression was significantly correlated with the TUNEL-positive cell number. CONCLUSIONS: Lower ASC expression correlates with clinical and pathological malignancy and, consequently, poor prognosis of OSCC. ASC has a close association with cell differentiation and apoptosis.

[952]

**TÍTULO / TITLE:** - A novel dendritic nanocarrier of polyamidoamine-polyethylene glycol-cyclic RGD for “smart” small interfering RNA delivery and in vitro antitumor effects by human ether-a-go-go-related gene silencing in anaplastic thyroid carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Nanomedicine. 2013;8:1293-306. doi: 10.2147/IJN.S41555. Epub 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago) [2147/IJN.S41555](#)

**AUTORES / AUTHORS:** - Li G; Hu Z; Yin H; Zhang Y; Huang X; Wang S; Li W

**INSTITUCIÓN / INSTITUTION:** - Department of Vascular and Thyroid Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, People’s Republic of China.

**RESUMEN / SUMMARY:** - The application of RNA interference techniques is promising in gene therapeutic approaches, especially for cancers. To improve safety and efficiency of small interfering RNA (siRNA) delivery, a triblock dendritic nanocarrier, polyamidoamine-polyethylene glycol-cyclic RGD (PAMAM-PEG-cRGD), was developed and studied as an siRNA vector targeting the human ether-a-go-go-related gene (hERG) in human anaplastic thyroid carcinoma cells. Structure characterization, particle size, zeta potential, and gel retardation assay confirmed that complete triblock components were successfully synthesized with effective binding capacity of siRNA in this triblock nanocarrier. Cytotoxicity data indicated that conjugation of PEG significantly alleviated cytotoxicity when compared with unmodified PAMAM. PAMAM-PEG-cRGD exerted potent siRNA cellular internalization in which transfection efficiency measured by flow cytometry was up to 68% when the charge ratio (N/P ratio) was 3.5. Ligand-receptor affinity together with electrostatic interaction should be involved in the nano-siRNA endocytosis mechanism and we then proved that attachment of cRGD enhanced cellular uptake via RGD-integrin recognition. Gene silencing was evaluated by reverse transcription polymerase chain reaction and PAMAM-PEG-cRGD-siRNA complex downregulated the expression of hERG to 26.3% of the control value. Furthermore, gene knockdown of hERG elicited growth suppression as well as activated apoptosis by means of abolishing vascular endothelial growth factor secretion and triggering caspase-3 cascade in anaplastic thyroid carcinoma cells. Our study demonstrates that this novel triblock polymer, PAMAM-PEG-cRGD, exhibits negligible cytotoxicity, effective transfection, “smart” cancer targeting, and therefore is a promising siRNA nanocarrier.

[953]

**TÍTULO / TITLE:** - Expression of DNA-PKcs and BRCA1 as prognostic indicators in nasopharyngeal carcinoma following intensity-modulated radiation therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1199-1204. Epub 2013 Feb 18.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1196](http://dx.doi.org/10.3892/ol.2013.1196)

**AUTORES / AUTHORS:** - Yang J; Xu X; Hao Y; Chen J; Lu H; Qin J; Peng L; Chen B

**INSTITUCIÓN / INSTITUTION:** - Cancer Center, Renmin Hospital of Wuhan University, Wuhan 430060; ; Department of Radiotherapy, Clinical Cancer Center, People's Hospital of Guangxi Autonomous Region, Nanning 530021, P.R. China.

**RESUMEN / SUMMARY:** - The mechanisms of radiation-induced effects in cancer mainly involve double-strand breaks (DSBs) which are important in maintaining the stability of genes. The DNA repair genes breast cancer 1 (BRCA1) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) are capable of maintaining genetic stability through two distinct and complementary repair mechanisms for DNA DSBs, known as repair-homologous recombination (HR) and non-homologous end joining (NHEJ). DNA-PKcs is a member of the phosphatidylinositol 3-kinase (PI3K) family. The PI3K/AKT cell signaling pathway is implicated in cell migration and invasion. The BRCA1 protein is implicated in multiple complex cellular processes that are related to chromosome sensitivity to mutagens. To determine the protein expression and clinical implications of DNA-PKcs and BRCA1 in nasopharyngeal carcinoma (NPC) and cancer progression, we evaluated its expression status by immunohistochemistry in 87 patients who received intensity-modulated radiation therapy (IMRT). In NPC, negative expression of DNA-PKcs was detected in 35 of the 87 (40.2%) cancer types and was significantly associated with poor patient survival ( $P < 0.05$ ). The overexpression of DNA-PKcs and BRCA1 also led to significantly improved distant metastasis-free survival compared with patients who did not overexpress both genes, although the expression level of BRCA1 and distant metastasis-free survival were not closely correlated. In addition, multivariate analysis indicated that DNA-PKcs status is a predictive marker of distant metastasis-free survival. In conclusion, lower expression of DNA-PKcs may be correlated with higher distant metastasis in patients with NPC. DNA-PKcs may be a predictive marker of distant metastasis after IMRT, independent of the classical prognostic marker. BRCA1 may additionally exert a synergistic effect to predict distant metastasis-free survival.

[954]

**TÍTULO / TITLE:** - Multiple Functions of the RNA-Binding Protein HuR in Cancer Progression, Treatment Responses and Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](http://dx.doi.org/10.3390/ijms140510015)

**REVISTA / JOURNAL:** - Int J Mol Sci. 2013 May 10;14(5):10015-41. doi: 10.3390/ijms140510015.

●●Enlace al texto completo (gratis o de pago) [3390/ijms140510015](http://dx.doi.org/10.3390/ijms140510015)

**AUTORES / AUTHORS:** - Wang J; Guo Y; Chu H; Guan Y; Bi J; Wang B

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, General Hospital, Jinan Command of the People's Liberation Army, Jinan 250031, China.

[gqjun2005@126.com](mailto:gqjun2005@126.com).

**RESUMEN / SUMMARY:** - The human embryonic lethal abnormal vision-like protein, HuR, is a member of the Hu family of RNA-binding proteins. Over the past decade, this ubiquitously expressed protein has been extensively investigated in cancer research because it is involved in the regulation of mRNA stability and translation in many cell types. HuR activity and function is associated with its subcellular distribution, transcriptional regulation, translational and post-translational modifications. HuR regulation of target mRNAs is based on the interaction between the three specific domains of HuR protein and one or several U- or AU-rich elements (AREs) in the untranslated region of target mRNAs. A number of cancer-related transcripts containing AREs, including mRNAs for proto-oncogenes, cytokines, growth factors, and invasion factors, have been characterized as HuR targets. It has been proposed that HuR has a central tumorigenic activity by enabling multiple cancer phenotypes. In this review, we comprehensively survey the existing evidence with regard to the diverse functions of HuR in cancer development and progression. The current data also suggest that HuR might be a novel and promising therapeutic target and a marker for treatment response and prognostic evaluation.

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[955]

**TÍTULO / TITLE:** - A novel biomarker-based analysis reliably predicts nodal metastases in anal carcinoma: preliminary evidence of therapeutic impact.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Colorectal Dis. 2013 May 21. doi: 10.1111/codi.12289.

●●Enlace al texto completo (gratis o de pago) [1111/codi.12289](http://1111/codi.12289)

**AUTORES / AUTHORS:** - Mistrangelo M; Senetta R; Racca P; Castellano I; Chiusa L; Bello M; Ricardi U; Morino M; Cassoni P

**INSTITUCIÓN / INSTITUTION:** - Digestive and Colorectal Surgery, Centre of Minimal Invasive Surgery, University of Turin, Molinette Hospital, Italy.

**RESUMEN / SUMMARY:** - AIM: Routine prophylactic inguinal irradiation in anal cancer may cause significant toxicity associated with overtreatment bias. The aim of this study was to determine the risk of regional node metastases in anal carcinoma by identifying predictive molecular biomarkers METHOD: Clinicohistopathological data from fifty pretreatment anal carcinomas biopsies were collected. Immunohistochemical analysis with antibodies against Ki67, p53, Epidermal Growth Factor Receptor (EGFR) and YKL-40 were performed. Statistical correlations between biomarkers and clinical-pathological features and outcomes were studied. Sentinel lymph node biopsy was performed in a subset of 36 patients RESULTS: All patients had undergone synchronous radio-chemotherapy; Tumour recurrence had developed in 26%, and 16% had died. YKL-40 tumor expression correlated with lymph node metastasis, whereas

no inguinal node metastases were found in any of the (14%) of patients presenting with a YKL-40/EGFR negative tumour. YKL-40 expression and node metastasis were both significantly associated with shorter overall and disease free survival. Tumour grade significantly correlated with DFS only. HIV, tumour histological type, Ki67, p53 and EGFR were not associated with outcome  
CONCLUSION: YKL-40 expression in anal carcinoma is correlated with a poor outcome and can predict lymph node metastases. The combined absence of YKL-40 and EGFR expression in a first biopsy of anal carcinoma reliably selects a subset of patients without inguinal metastases. Such patients could be spared sentinel lymph node biopsy and/or inguinal radiotherapy. This article is protected by copyright. All rights reserved.

[956]

**TÍTULO / TITLE:** - Preclinical Safety, Toxicology, and Biodistribution Study of Adenoviral Gene Therapy with sVEGFR-2 and sVEGFR-3 Combined with Chemotherapy for Ovarian Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Gene Ther Clin Dev. 2013 Mar;24(1):29-37. doi: 10.1089/humc.2013.006. Epub 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago) [1089/humc.2013.006](#)

**AUTORES / AUTHORS:** - Tuppurainen L; Sallinen H; Kokki E; Koponen J; Anttila M; Pulkkinen K; Heikura T; Toivanen P; Hamalainen K; Kosma VM; Heinonen S; Alitalo K; Yla-Herttuala S

**INSTITUCIÓN / INSTITUTION:** - 1 Department of Molecular Medicine, A.I. Virtanen Institute, University of Eastern Finland, Kuopio, FIN-70211, Finland.

**RESUMEN / SUMMARY:** - Abstract Antiangiogenic and antilymphangiogenic gene therapy with soluble vascular endothelial growth factor receptor-2 (VEGFR-2) and soluble VEGFR-3 in combination with chemotherapy is a potential new treatment for ovarian carcinoma. We evaluated the safety, toxicology, and biodistribution of intravenous AdsVEGFR-2 and AdsVEGFR-3 combined with chemotherapy in healthy rats (n=90) before entering a clinical setting. The study groups were: AdLacZ and AdLacZ with chemotherapy as control groups, low dose AdsVEGFR-2 and AdsVEGFR-3, high dose AdsVEGFR-2 and AdsVEGFR-3, combination of low dose AdsVEGFR-2 and AdsVEGFR-3 with chemotherapy, combination of high dose AdsVEGFR-2 and AdsVEGFR-3 with chemotherapy, and chemotherapy only. The follow-up time was 4 weeks. Safety and toxicology were assessed by monitoring the clinical status of the animals and by histological, hematological, and clinical chemistry parameters. For the biodistribution studies, quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA) were used. Low dose ( $2 \times 10^{10}$  vp) AdsVEGFR-2 and AdsVEGFR-3 gene therapy was well tolerated, even when gene therapy was combined with chemotherapy. Notably, only transient elevation of liver enzymes and mild regenerative

changes were seen in liver after the gene transfer in the groups that received high doses ( $2 \times 10^{11}$  vp) of Ad<sub>s</sub>VEGFR-2 and Ad<sub>s</sub>VEGFR-3 with or without chemotherapy. No life-threatening adverse effects were noticed in any of the treatment groups. The highest protein concentration of soluble VEGFR-2 (sVEGFR-2) in circulation was seen 1 week after the gene transfer. The combination of chemotherapy to gene therapy seemed to prolong the time of detectable transgene protein at least 1 week in the circulation. The expression of Ad<sub>s</sub>VEGFR-2 and Ad<sub>s</sub>VEGFR-3 transgenes was mainly seen in the liver and spleen as detected by qRT-PCR. According to these results, Ad<sub>s</sub>VEGFR-2 and Ad<sub>s</sub>VEGFR-3 gene therapy combined with chemotherapy is safe and can be brought to clinical testing in ovarian cancer patients.

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[957]

**TÍTULO / TITLE:** - The Natural Human IgM Antibody PAT-SM6 Induces Apoptosis in Primary Human Multiple Myeloma Cells by Targeting Heat Shock Protein GRP78.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 7;8(5):e63414. doi: 10.1371/journal.pone.0063414. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063414](#)

**AUTORES / AUTHORS:** - Rasche L; Duell J; Morgner C; Chatterjee M; Hensel F; Rosenwald A; Einsele H; Topp MS; Brandlein S

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany.

**RESUMEN / SUMMARY:** - In contrast to other haematological malignancies, targeted immunotherapy has not entered standard treatment regimens for de novo or relapsed multiple myeloma (MM) yet. While a number of IgG-formatted monoclonal antibodies are currently being evaluated in clinical trials in MM, our study aimed to investigate whether the fully human IgM monoclonal antibody PAT-SM6 that targets a tumour-specific variant of the heat shock protein GRP78 might be an attractive candidate for future immunotherapeutic approaches. We here show that GRP78 is stably and consistently expressed on the surface on tumour cells from patients with de novo, but also relapsed MM and that binding of PAT-SM6 to MM cells can specifically exert cytotoxic effects on malignant plasma cells, whereas non-malignant cells are not targeted. We demonstrate that the induction of apoptosis and, to a lesser extent, complement dependent cytotoxicity is the main mode of action of PAT-SM6, whereas antibody dependent cellular cytotoxicity does not appear to contribute to the cytotoxic properties of this antibody. Given the favourable safety profile of PAT-SM6 in monkeys, but also in a recent phase I trial in patients with malignant melanoma, our results form the basis for a planned phase I study in patients with relapsed MM.

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[958]

**TÍTULO / TITLE:** - Androgen receptor decreases the cytotoxic effects of chemotherapeutic drugs in upper urinary tract urothelial carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1325-1330. Epub 2013 Jan 18.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1140](#)

**AUTORES / AUTHORS:** - Hsieh TF; Chen CC; Yu AL; Ma WL; Zhang C; Shyr CR; Chang C

**INSTITUCIÓN / INSTITUTION:** - Division of Urology, Department of Surgery, Buddhist Tzu Chi General Hospital, Taichung Branch, Taichung 40427;

**RESUMEN / SUMMARY:** - Upper urinary tract urothelial carcinomas (UUTUCs) represent relatively uncommon yet devastating tumors that affect more males than females. However, the correlation between gender difference and disease progression remains unclear. Androgen and the androgen receptor (AR) were previously hypothesized to account for the gender difference in the incidence of urothelial carcinomas; however, the role of AR in the development and progression of UUTUCs is not well understood. In addition, although UUTUCs are responsive to chemotherapy, various responses are presented among patients. Therefore, the aim of the present study was to determine the role of AR in the response of UUTUC cells to chemotherapeutic drugs. In this study, AR overexpression in UUTUC cells (BFTC 909) was identified to reduce the cytotoxic effect of chemotherapeutic drugs, including doxorubicin, cisplatin and mitomycin C and protected cells from drug-induced death. The expression of ABCG2, an ATP-binding cassette half-transporter associated with multidrug resistance, was increased in AR-overexpressing BFTC cells. In addition, use of the AR degradation enhancer, ASC-J9®, repressed the AR effect on increasing cell viability under drug treatment. In summary, results of the present study indicate that the status of AR expression levels in UUTUCs may be a significant factor in affecting the efficacy of chemotherapy and classic chemotherapeutic drugs and AR targeted therapy may provide a novel potential therapeutic approach to improve treatment of UUTUCs.

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[959]

**TÍTULO / TITLE:** - Hepatitis C virus core protein down-regulates p21(Waf1/Cip1) and inhibits curcumin-induced apoptosis through microRNA-345 targeting in human hepatoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(4):e61089. doi: 10.1371/journal.pone.0061089. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061089](#)

**AUTORES / AUTHORS:** - Shiu TY; Huang SM; Shih YL; Chu HC; Chang WK; Hsieh TY

**INSTITUCIÓN / INSTITUTION:** - Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, ROC.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Hepatitis C virus (HCV) has been reported to regulate cellular microRNAs. The HCV core protein is considered to be a potential oncoprotein in HCV-related hepatocellular carcinoma, but HCV core-modulated cellular microRNAs are unknown. The HCV core protein regulates p21(Waf1/Cip1) expression. However, the mechanism of HCV core-associated p21(Waf1/Cip1) regulation remains to be further clarified. Therefore, we attempted to determine whether HCV core-modulated cellular microRNAs play an important role in regulating p21(Waf1/Cip1) expression in human hepatoma cells. **METHODS:** Cellular microRNA profiling was investigated in core-overexpressing hepatoma cells using TaqMan low density array. Array data were further confirmed by TaqMan real-time qPCR for single microRNA in core-overexpressing and full-length HCV replicon-expressing cells. The target gene of microRNA was examined by reporter assay. The gene expression was determined by real-time qPCR and Western blotting. Apoptosis was examined by annexin V-FITC apoptosis assay. Cell cycle analysis was performed by propidium iodide staining. Cell proliferation was analyzed by MTT assay. **RESULTS:** HCV core protein up- or down-regulated some cellular microRNAs in Huh7 cells. HCV core-induced microRNA-345 suppressed p21(Waf1/Cip1) gene expression through targeting its 3' untranslated region in human hepatoma cells. Moreover, the core protein inhibited curcumin-induced apoptosis through p21(Waf1/Cip1)-targeting microRNA-345 in Huh7 cells. **CONCLUSION AND SIGNIFICANCE:** HCV core protein enhances the expression of microRNA-345 which then down-regulates p21(Waf1/Cip1) expression. It is the first time that HCV core protein has ever been shown to suppress p21(Waf1/Cip1) gene expression through miR-345 targeting.

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[960]

**TÍTULO / TITLE:** - CG0009, a novel glycogen synthase kinase 3 inhibitor, induces cell death through cyclin D1 depletion in breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(4):e60383. doi: 10.1371/journal.pone.0060383. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060383](http://1371/journal.pone.0060383)

**AUTORES / AUTHORS:** - Kim HM; Kim CS; Lee JH; Jang SJ; Hwang JJ; Ro S; Choi J

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - Glycogen synthase kinase 3 $\alpha$ /beta (GSK3 $\alpha$ /beta) is a constitutively active serine/threonine kinase involved in multiple physiological processes, such as protein synthesis, stem cell maintenance and apoptosis, and acts as a key suppressor of the Wnt-beta-

catenin pathway. In the present study, we examined the therapeutic potential of a novel GSK3 inhibitor, CG0009, in the breast cancer cell lines, BT549, HS578T, MDA-MB-231, NCI/ADR-RES, T47D, MCF7 and MDA-MB-435, from the NCI-60 cancer cell line panel. Assessment of cytotoxicity, apoptosis and changes in estrogen-signaling proteins was performed using cell viability assays, Western blotting and quantitative real-time PCR. CG0009 enhanced the inactivating phosphorylation of GSK3alpha at Ser21 and GSK3beta at Ser9 and simultaneously decreased activating phosphorylation of GSK3beta at Tyr216, and induced caspase-dependent apoptosis independently of estrogen receptor alpha (ERalpha) expression status, which was not observed with the other GSK3 inhibitors examined, including SB216763, kenpaullone and LiCl. CG0009 treatment (1 micromol/L) completely ablated cyclin D1 expression in a time-dependent manner in all the cell lines examined, except T47D. CG0009 alone significantly activated p53, leading to relocation of p53 and Bax to the mitochondria. GSK3 inhibition by CG0009 led to slight upregulation of the beta-catenin target genes, c-Jun and c-Myc, but not cyclin D1, indicating that CG0009-mediated cyclin D1 depletion overwhelms the pro-survival signal of beta-catenin, resulting in cell death. Our findings suggest that the novel GSK3 inhibitor, CG0009, inhibits breast cancer cell growth through cyclin D1 depletion and p53 activation, and may thus offer an innovative therapeutic approach for breast cancers resistant to hormone-based therapy.

[961]

**TÍTULO / TITLE:** - Prognostic predictive values of gemcitabine sensitivity-related gene products for unresectable or recurrent biliary tract cancer treated with gemcitabine alone.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg Oncol. 2013 May 27;11:117. doi: 10.1186/1477-7819-11-117.

●●Enlace al texto completo (gratis o de pago) [1186/1477-7819-11-117](#)

**AUTORES / AUTHORS:** - Murata A; Amano R; Yamada N; Kimura K; Yashiro M; Nakata B; Hirakawa K

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**RESUMEN / SUMMARY:** - BACKGROUND: Gemcitabine is a pyrimidine nucleoside analog that is a commonly used chemotherapeutic agent for unresectable or recurrent biliary tract cancer (BTC). Several molecules involved in gemcitabine metabolism, including human equilibrative nucleoside transporter (hENT1), deoxycytidine kinase (dCK), and ribonucleotide reductase subunit M1 (RRM1), have been investigated as predictive biomarkers of gemcitabine efficacy, mostly in pancreatic cancer. The aim of this study is to clarify which biomarker is the most reliable among hENT1, dCK, and RRM1 to predict survival in patients with advanced BTC treated with gemcitabine alone.

**METHODS:** The analysis was performed on samples from 28 patients with unresectable or recurrent BTC who were treated with gemcitabine alone as first-line therapy. The starting date of overall survival (OS) and progression-free survival (PFS) was defined as the date of first treatment with gemcitabine. Intratumoral hENT1, dCK, and RRM1 expressions were examined by immunohistochemistry. **RESULTS:** The expressions of hENT1, dCK, and RRM1 had no significant relationships with age, gender, primary tumor site, recurrence/unresectable, or histological type. Among the three molecules, only hENT1 expression was a significant factor affecting OS and PFS in univariate analysis; OS was 11.4 months for high hENT1 expression versus 5.7 months for low,  $P = 0.0057$ ; PFS was 7.7 months for high versus 2.5 months for low,  $P = 0.0065$ . Multivariate analyses also identified hENT1 expression as an independent predictive factor for OS. **CONCLUSIONS:** hENT1 is the most reliable predictive marker of survival in patients with advanced BTC treated with gemcitabine.

[962]

**TÍTULO / TITLE:** - Apoptosis Induction of Human Bladder Cancer Cells by Sanguinarine through Reactive Oxygen Species-Mediated Up-Regulation of Early Growth Response Gene-1.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 22;8(5):e63425. doi: 10.1371/journal.pone.0063425. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063425](http://1371/journal.pone.0063425)

**AUTORES / AUTHORS:** - Han MH; Park C; Jin CY; Kim GY; Chang YC; Moon SK; Kim WJ; Choi YH

**INSTITUCIÓN / INSTITUTION:** - Anti-Aging Research Center & Blue-Bio Industry RIC, Dongeui University, Busan, Republic of Korea ; Department of Biochemistry, Dongeui University College of Oriental Medicine, Busan, Republic of Korea.

**RESUMEN / SUMMARY:** - Although the effects of sanguinarine, a benzophenanthridine alkaloid, on the inhibition of some kinds of cancer cell growth have been established, the underlying mechanisms are not completely understood. This study investigated possible mechanisms by which sanguinarine exerts its anticancer action in cultured human bladder cancer cell lines (T24, EJ, and 5637). Sanguinarine treatment resulted in concentration-response growth inhibition of the bladder cancer cells by inducing apoptosis. Sanguinarine-induced apoptosis was correlated with the up-regulation of Bax, the down-regulation of Bid and XIAP, the activation of caspases (-3, -8, and -9), and the generation of increased reactive oxygen species (ROS). The ROS scavenger N-acetyl cysteine (NAC) completely reversed the sanguinarine-triggered apoptotic events. In addition, sanguinarine effectively increased the activation of the c-Jun N-terminal kinase (JNK) and the expression of the early

growth response gene-1 (Egr-1), which was recovered by pretreatment with NAC. Furthermore, knockdown of Egr-1 expression by small interfering RNA attenuated sanguinarine-induced apoptosis, but not the JNK inhibitor, indicating that the interception of ROS generation blocked the sanguinarine-induced apoptotic effects via deregulation of the expression of Egr-1 proteins. Taken together, the data provide evidence that sanguinarine is a potent anticancer agent, which inhibits the growth of bladder cancer cells and induces their apoptosis through the generation of free radicals.

[963]

**TÍTULO / TITLE:** - Update of epidermal growth factor receptor-tyrosine kinase inhibitors in non-small-cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Chin Med Assoc. 2013 May;76(5):249-57. doi: 10.1016/j.jcma.2013.01.010. Epub 2013 Mar 22.

●●Enlace al texto completo (gratis o de pago) [1016/j.jcma.2013.01.010](http://1016/j.jcma.2013.01.010)

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**INSTITUCIÓN / INSTITUTION:** - Department of Chest Medicine, Taipei Veterans General Hospital, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC. Electronic address: [ymchen@vghtpe.gov.tw](mailto:ymchen@vghtpe.gov.tw).

**RESUMEN / SUMMARY:** - Lung cancer is the leading cause of cancer-related death in the world. Prior to the era of targeted therapy, platinum-based doublet chemotherapy was the first-line therapy of choice for patients with metastatic non-small-cell lung cancer (NSCLC). The availability of agents that target epidermal growth factor receptor (EGFR)-tyrosine kinase, as well as inhibitors against anaplastic lymphoma kinase (ALK) gene rearrangement or ROS-1 gene rearrangement product, has provided promising clinical benefits in specific subpopulations of NSCLC. At present, only first-generation EGFR-tyrosine kinase inhibitors (TKIs) (erlotinib and gefitinib) are available for clinical use. Second-generation irreversible EGFR-TKIs, such as afatinib, are still in clinical trials. In current clinical practice, EGFR-TKI is the first-line treatment of choice for metastatic NSCLC patients with tumor EGFR mutation or as salvage therapy in NSCLC patients who received systemic chemotherapy previously. Platinum-based doublet chemotherapy continues to be the standard of care for those treatment-naïve patients with EGFR wild-type tumor or unknown EGFR status. Even though all investigators agree with the use of EGFR-TKI as the first-line treatment in tumor EGFR-mutated patients, only 10-30% of NSCLC patients have mutated EGFR, and there was no obvious survival difference when EGFR-TKIs were used in a second-line setting versus a first-line treatment in EGFR-mutated patients. Thus, the molecular complexity of lung cancer emphasizes the need for optimizing treatment by seeking a more personalized approach to care, including searching for driver oncogenes, managing the emergence of resistance and overcoming that resistance, and optimizing the sequence of treatment. Numerous other novel targeted agents are now in

clinical development, including new agents targeting novel pathways and those that may have the potential to overcome the limitations or resistance associated with currently available EGFR-TKIs. In this report, we review the clinical data of EGFR-TKIs as molecular-targeted therapies in NSCLC.

[964]

**TÍTULO / TITLE:** - Metformin inhibits proliferation and promotes apoptosis of HER2 positive breast cancer cells by downregulating HSP90.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J BUON. 2013 Jan-Mar;18(1):51-6.

**AUTORES / AUTHORS:** - Tian-Wen C; Ya-Nan L; Duo F; Lin-Yu T; Ke Q; Hao-Yun Z; Hong-Xian W; Qiu-Sheng L; Heng K

**INSTITUCIÓN / INSTITUTION:** - Department of Thyroid and Breast Surgery, Affiliated Nanshan Hospital of Guangdong Medical College, Shenzhen, China.

**RESUMEN / SUMMARY:** - Purpose: To investigate the effects and the possible molecular mechanisms of metformin on HER2 positive breast cancer cells. Methods: SK-BR-3 HER2 positive breast cancer cells were treated with different concentrations of metformin. The growth inhibitory rate of the cells was calculated by MTT assay, apoptosis was detected by flow cytometry, and the expression level of heat shock protein 90 (HSP90) was performed by Western blot analysis. A control group consisted of cells treated with PBS. Results: With increased concentrations of metformin, cell growth inhibitory rates increased. The growth inhibitory rates with 0.5 mM, 2mM or 8mM metformin were significantly higher compared with the control group ( $p < 0.05$ ). Apoptosis in the metformin treated cells was also significantly higher compared with the control group ( $p = 0.003$ ). The expression level of HSP90 in the metformin group was significantly lower than that in the control group. Conclusion: Metformin can inhibit the proliferation and promote apoptosis of HER2 positive breast cancer cells, which is maybe related to inhibition of HSP90.

[965]

**TÍTULO / TITLE:** - Everolimus enhances the cytotoxicity of bendamustine in multiple myeloma cells through a network of pro-apoptotic and cell-cycle-progression regulatory proteins.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Biochim Biophys Sin (Shanghai). 2013 May 20.

●●Enlace al texto completo (gratis o de pago) [1093/abbs/gmt054](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China.

**RESUMEN / SUMMARY:** - Bendamustine is a bifunctional alkylating agent with some efficacy in the treatment of newly diagnosed and relapsed/refractory multiple myeloma (MM). Everolimus, an mammalian target of rapamycin

(mTOR) inhibitor, is an additional promising chemotherapeutic agent that has efficacy in a variety of cancers. We investigated the individual and combinational cytotoxic effects of these drugs in MM cell lines (RPMI8226 and MM1.S) and primary MM cells. Our results demonstrated a synergistic effect of these drugs, which was effective for both p53-wild-type and p-53-deleted MM cells, but was minimal in mononuclear cells from a healthy donor. Combination treatment with the two agents inhibited proliferation and promoted cytotoxicity and apoptosis as assessed by Annexin-V/PI staining, caspase-3 degradation, and PARP cleavage. Cell death was associated with the up-regulation of the pro-apoptotic protein Bax and the down-regulation of the anti-apoptotic proteins Mcl-1 and survivin. The combination drug treatment also promoted a decrease in the levels of the downstream target proteins of the mTOR pathway, p70s6k, and 4EBP-1, as well as an increase in the level of phosphorylation of the tumor suppressor protein p53 in MM1.S cells. p21 was also down-regulated upon treatment with the two drugs, suggesting a mechanism of sensitization through the release of cell cycle arrest. Our results demonstrate a network of regulatory factors that may contribute to the synergistic cytotoxicity of everolimus and bendamustine, and provide a rationale for application for the combinatorial treatment of MM with alkylating agents and mTOR inhibitors in future clinical practice.

[966]

**TÍTULO / TITLE:** - Stable gene-silence of Kif2a synergistic with 5-fluorouracil suppresses oral tongue squamous cell carcinoma growth in vitro and in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Apr 6. pii: S2212-4403(13)00059-X. doi: 10.1016/j.oooo.2013.01.028.

●●Enlace al texto completo (gratis o de pago) [1016/j.oooo.2013.01.028](http://1016/j.oooo.2013.01.028)

**AUTORES / AUTHORS:** - Wang CQ; Li YJ; Wei ZM; Zhu CJ; Qu X; Wei FC; Xing XM; Yu WJ

**INSTITUCIÓN / INSTITUTION:** - Lecturer, Department of Pathology, Medical College of Qingdao University.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Squamous cell carcinoma of the oral tongue (SCCOT) is one of the most common malignant carcinomas in the head and neck. Recurrence and/or metastasis often results in failure of treatment and decreases the survival of the patients. The purpose of this study is to investigate the effect of gene-silence of Kif2a on SCCOT in viro and in vivo. **STUDY DESIGN:** Plasmid-mediated expression of Kif2a-siRNA (pGPU6/GFP/Kif2a) was employed to silence the expression of Kif2a in Tca8113 cells at both mRNA and protein levels. Tca8113 cell proliferation was measured by 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay and growth of Tca8113 tumors was determined by intra-tumor injection of pGPU6/GFP/Kif2a in nude mice. **RESULTS:** Gene-silence of Kif2a suppressed Tca8113 cell proliferation. pGPU6/GFP/Kif2a synergized the tumor

suppression effect of 5-Fluorouracil (5-Fu) on Tca8113 cells. CONCLUSIONS: Our data support that Kif2a is a potential molecular target for the therapeutics of recurrent and metastatic SCCOT.

[967]

**TÍTULO / TITLE:** - Circulating tumour cells and cell-free DNA as tools for managing breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nat Rev Clin Oncol. 2013 May 28. doi: 10.1038/nrclinonc.2013.80.

●●Enlace al texto completo (gratis o de pago) [1038/nrclinonc.2013.80](#)

**AUTORES / AUTHORS:** - De Mattos-Arruda L; Cortes J; Santarpia L; Vivancos A; Tabernero J; Reis-Filho JS; Seoane J

**INSTITUCIÓN / INSTITUTION:** - Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Paseo Vall d'Hebron 119-129, 08035 Barcelona, España.

**RESUMEN / SUMMARY:** - Circulating blood biomarkers promise to become non-invasive real-time surrogates for tumour tissue-based biomarkers. Circulating biomarkers have been investigated as tools for breast cancer diagnosis, the dissection of breast cancer biology and its genetic and clinical heterogeneity, prognostication, prediction and monitoring of therapeutic response and resistance. Circulating tumour cells and cell-free plasma DNA have been analysed in retrospective studies, and the assessment of these biomarkers is being incorporated into clinical trials. As the scope of breast cancer intratumour genetic heterogeneity unravels, the development of robust and standardized methods for the assessment of circulating biomarkers will be essential for the realization of the potentials of personalized medicine. In this Review, we discuss the current status of blood-born biomarkers as surrogates for tissue-based biomarkers, and their burgeoning impact on the management of patients with breast cancer.

[968]

**TÍTULO / TITLE:** - Rapid cytotoxicity of antimicrobial peptide tempopin-1CEa in breast cancer cells through membrane destruction and intracellular calcium mechanism.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(4):e60462. doi: 10.1371/journal.pone.0060462. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060462](#)

**AUTORES / AUTHORS:** - Wang C; Tian LL; Li S; Li HB; Zhou Y; Wang H; Yang QZ; Ma LJ; Shang DJ

**INSTITUCIÓN / INSTITUTION:** - Liaoning Provincial Key Laboratory of Biotechnology and Drug Discovery, Liaoning Normal University, Dalian, China.

**RESUMEN / SUMMARY:** - Temporin-1CEa is an antimicrobial peptide isolated from the skin secretions of the Chinese brown frog (*Rana chensinensis*). We have previously reported the rapid and broad-spectrum anticancer activity of temporin-1CEa *in vitro*. However, the detailed mechanisms for temporin-1CEa-induced cancer cell death are still weakly understood. In the present study, the mechanisms of temporin-1CEa-induced rapid cytotoxicity on two human breast cancer cell lines, MDA-MB-231 and MCF-7, were investigated. The MTT assay and the LDH leakage assay indicated that one-hour of incubation with temporin-1CEa led to cytotoxicity in a dose-dependent manner. The morphological observation using electronic microscopes suggested that one-hour exposure of temporin-1CEa resulted in profound morphological changes in both MDA-MB-231 and MCF-7 cells. The membrane-disrupting property of temporin-1CEa was further characterized by induction of cell-surface exposure of phosphatidylserine, elevation of plasma membrane permeability and rapid depolarization of transmembrane potential. Moreover, temporin-1CEa evoked intracellular calcium ion and reactive oxygen species (ROS) elevations as well as collapse of mitochondrial membrane potential (Deltaphim). In summary, the present study indicates that temporin-1CEa triggers rapid cell death in breast cancer cells. This rapid cytotoxic activity might be mediated by both membrane destruction and intracellular calcium mechanism.

[969]

**TÍTULO / TITLE:** - Downregulation of miRNA-31 induces taxane resistance in ovarian cancer cells through increase of receptor tyrosine kinase MET.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Oncogenesis*. 2013 Mar 25;2:e40. doi: 10.1038/oncsis.2013.3.

●●Enlace al texto completo (gratis o de pago) [1038/oncsis.2013.3](#)

**AUTORES / AUTHORS:** - Mitamura T; Watari H; Wang L; Kanno H; Hassan MK; Miyazaki M; Katoh Y; Kimura T; Tanino M; Nishihara H; Tanaka S; Sakuragi N

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Sapporo, Japan [2] Department of Cancer Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

**RESUMEN / SUMMARY:** - Ovarian cancer is one of the most aggressive female reproductive tract tumors. Paclitaxel (PTX) is widely used for the treatment of ovarian cancer. However, ovarian cancers often acquire chemotherapeutic resistance to this agent. We investigated the mechanism of chemoresistance by analysis of microRNAs using the ovarian cancer cell line KFr13 and its PTX-resistant derivative (KFr13Tx). We found that miR-31 was downregulated in KFr13Tx cells, and that re-introduction of miR31 re-sensitized them to PTX both *in vitro* and *in vivo*. miR-31 was found to bind to the 3'-UTR of mRNA of MET, and the decrease in MET correlated to higher sensitivity to PTX. Furthermore, co-treatment of KFr13Tx cells with MET inhibitors sensitized the tumor cells to

PTX both in vitro and in vivo. In addition, lower levels of miR31 and higher expression of MET in human ovarian cancer specimens were significantly correlated with PTX chemoresistance and poor prognosis. This study demonstrated miR31-dependent regulation of MET for chemoresistance of ovarian cancer, raising the possibility that combination therapy with a MET inhibitor and PTX will increase PTX efficacy.

[970]

**TÍTULO / TITLE:** - Hypoxia counteracts taxol-induced apoptosis in MDA-MB-231 breast cancer cells: role of autophagy and JNK activation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 May 16;4:e638. doi: 10.1038/cddis.2013.167.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.167](#)

**AUTORES / AUTHORS:** - Notte A; Ninane N; Arnould T; Michiels C

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Biochemistry and Cellular Biology, NARILIS, University of Namur-FUNDP, Namur, Belgium.

**RESUMEN / SUMMARY:** - Cancer cell resistance against chemotherapy is still a heavy burden to improve anticancer treatments. Autophagy activation and the development of hypoxic regions within the tumors are known to promote cancer cell resistance. Therefore, we sought to evaluate the role of autophagy and hypoxia on the taxol-induced apoptosis in MDA-MB-231 breast cancer cells. The results showed that taxol induced apoptosis after 16 h of incubation, and that hypoxia protected MDA-MB-231 cells from taxol-induced apoptosis. In parallel, taxol induced autophagy activation already after 2 h of incubation both under normoxia and hypoxia. Autophagy activation after taxol exposure was shown to be a protective mechanism against taxol-induced cell death both under normoxia and hypoxia. However, at longer incubation time, the autophagic process reached a saturation point under normoxia leading to cell death, whereas under hypoxia, autophagy flow still correctly took place allowing the cells to survive. Autophagy induction is induced after taxol exposure via mechanistic target of rapamycin (mTOR) inhibition, which is more important in cells exposed to hypoxia. Taxol also induced c-Jun N-terminal kinase (JNK) activation and phosphorylation of its substrates B-cell CLL/lymphoma 2 (Bcl2) and BCL2-like 1 (BclXL) under normoxia and hypoxia very early after taxol exposure. Bcl2 and BclXL phosphorylation was decreased more importantly under hypoxia after long incubation time. The role of JNK in autophagy and apoptosis induction was studied using siRNAs. The results showed that JNK activation promotes resistance against taxol-induced apoptosis under normoxia and hypoxia without being involved in induction of autophagy. In conclusion, the resistance against taxol-induced cell death observed under hypoxia can be explained by a more effective autophagic flow activated via the classical mTOR pathway and by a mechanism involving JNK, which could be dependent on Bcl2

and BclXL phosphorylation but independent of JNK-induced autophagy activation.

[971]

**TÍTULO / TITLE:** - Autophagy inhibition enhances apigenin-induced apoptosis in human breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin J Cancer Res. 2013 Apr;25(2):212-22. doi: 10.3978/j.issn.1000-9604.2013.04.01.

●●Enlace al texto completo (gratis o de pago) [3978/j.issn.1000-9604.2013.04.01](#)

**AUTORES / AUTHORS:** - Cao X; Liu B; Cao W; Zhang W; Zhang F; Zhao H; Meng R; Zhang L; Niu R; Hao X; Zhang B

**INSTITUCIÓN / INSTITUTION:** - National Key Laboratory of Breast Cancer Prevention and Treatment, Tianjin Medical University, Tianjin 300060, China ; Department of Breast Cancer Surgery of the Cancer Hospital, Tianjin Medical University, Tianjin 300060, China.

**RESUMEN / SUMMARY:** - Apigenin (4',5,7-trihydroxyflavone) is a member of the flavone subclass of flavonoids present in fruits and vegetables. The involvement of autophagy in the apigenin-induced apoptotic death of human breast cancer cells was investigated. Cell proliferation and viability were assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and clonogenic assays. Flow cytometry, fluorescent staining and Western blot analysis were employed to detect apoptosis and autophagy, and the role of autophagy was assessed using autophagy inhibitors. Apigenin dose- and time-dependently repressed the proliferation and clonogenic survival of the human breast cancer T47D and MDA-MB-231 cell lines. The death of T47D and MDA-MB-231 cells was due to apoptosis associated with increased levels of Caspase3, PARP cleavage and Bax/Bcl-2 ratios. The results from flow cytometry and fluorescent staining also verified the occurrence of apoptosis. In addition, the apigenin-treated cells exhibited autophagy, as characterized by the appearance of autophagosomes under fluorescence microscopy and the accumulation of acidic vesicular organelles (AVOs) by flow cytometry. Furthermore, the results of the Western blot analysis revealed that the level of LC3-II, the processed form of LC3-I, was increased. Treatment with the autophagy inhibitor, 3-methyladenine (3-MA), significantly enhanced the apoptosis induced by apigenin, which was accompanied by an increase in the level of PARP cleavage. Similar results were also confirmed by flow cytometry and fluorescence microscopy. These results indicate that apigenin has apoptosis- and autophagy-inducing effects in breast cancer cells. Autophagy plays a cytoprotective role in apigenin-induced apoptosis, and the combination of apigenin and an autophagy inhibitor may be a promising strategy for breast cancer control.

[972]

**TÍTULO / TITLE:** - Equol enhances tamoxifen's anti-tumor activity by induction of caspase-mediated apoptosis in MCF-7 breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 15;13:238. doi: 10.1186/1471-2407-13-238.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-238](#)

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**RESUMEN / SUMMARY:** - BACKGROUND: Soy phytoestrogens, such as daidzein and its metabolite equol, have been proposed to be responsible for the low breast cancer rate in Asian women. Since the majority of estrogen receptor positive breast cancer patients are treated with tamoxifen, the basic objective of this study is to determine whether equol enhances tamoxifen's anti-tumor effect, and to identify the molecular mechanisms involved. METHODS: For this purpose, we examined the individual and combined effects of equol and tamoxifen on the estrogen-dependent MCF-7 breast cancer cells using viability assays, annexin-V/PI staining, cell cycle and western blot analysis. RESULTS: We found that equol (>50 µM) and 4-hydroxy-tamoxifen (4-OHT; >100 nM) significantly reduced the MCF-7 cell viability. Furthermore, the combination of equol (100 µM) and 4-OHT (10 µM) induced apoptosis more effectively than each compound alone. Subsequent treatment of MCF-7 cells with the pan-caspase inhibitor Z-VAD-FMK inhibited equol- and 4-OHT-mediated apoptosis, which was accompanied by PARP and alpha-fodrin cleavage, indicating that apoptosis is mainly caspase-mediated. These compounds also induced a marked reduction in the bcl-2:bax ratio, which was accompanied by caspase-9 and caspase-7 activation and cytochrome-c release to the cytosol. Taken together, these data support the notion that the combination of equol and tamoxifen activates the intrinsic apoptotic pathway more efficiently than each compound alone. CONCLUSIONS: Consequently, equol may be used therapeutically in combination treatments and clinical studies to enhance tamoxifen's effect by providing additional protection against estrogen-responsive breast cancers.

[973]

**TÍTULO / TITLE:** - 2,2'-diphenyl-3,3'-diindolylmethane: a potent compound induces apoptosis in breast cancer cells by inhibiting EGFR pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e59798. doi: 10.1371/journal.pone.0059798. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0059798](#)

**AUTORES / AUTHORS:** - Bhowmik A; Das N; Pal U; Mandal M; Bhattacharya S; Sarkar M; Jaisankar P; Maiti NC; Ghosh MK

**INSTITUCIÓN / INSTITUTION:** - Division of Cancer Biology and Inflammatory Disorder, Council of Scientific and Industrial Research (CSIR)-Indian Institute of Chemical Biology (IICB), Kolkata, West Bengal, India.

**RESUMEN / SUMMARY:** - Despite recent advances in medicine, 30-40% of patients with breast cancer show recurrence underscoring the need for improved effective therapy. In this study, by in vitro screening we have selected a novel synthetic indole derivative 2,2'-diphenyl-3,3'-diindolylmethane (DPDIM) as a potential anti-breast cancer agent. DPDIM induces apoptosis both in vitro in breast cancer cells MCF7, MDA-MB 231 and MDA-MB 468 and in vivo in 7,12-dimethylbenz[alpha]anthracene (DMBA) induced Sprague-Dawley (SD) rat mammary tumor. Our in vitro studies show that DPDIM exerts apoptotic effect by negatively regulating the activity of EGFR and its downstream molecules like STAT3, AKT and ERK1/2 which are involved in the proliferation and survival of these cancer cells. In silico predictions also suggest that DPDIM may bind to EGFR at its ATP binding site. DPDIM furthermore inhibits EGF induced increased cell viability. We have also shown decreased expression of pro-survival factor Bcl-XL as well as increase in the level of pro-apoptotic proteins like Bax, Bad, Bim in DPDIM treated cells in vitro and in vivo. Our results further indicate that the DPDIM induced apoptosis is mediated through mitochondrial apoptotic pathway involving the caspase-cascade. To the best of our knowledge this is the first report of DPDIM for its anticancer activity. Altogether this report suggests that DPDIM could be an effective therapeutic agent for breast cancer.

[974]

**TÍTULO / TITLE:** - Heat Shock Protein 90 Inhibitors Repress Latent Membrane Protein 1 (LMP1) Expression and Proliferation of Epstein-Barr Virus-Positive Natural Killer Cell Lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 3;8(5):e63566. doi: 10.1371/journal.pone.0063566. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063566](http://dx.doi.org/10.1371/journal.pone.0063566)

**AUTORES / AUTHORS:** - Murata T; Iwata S; Siddiquey MN; Kanazawa T; Goshima F; Kawashima D; Kimura H; Tsurumi T

**INSTITUCIÓN / INSTITUTION:** - Division of Virology, Aichi Cancer Center Research Institute, Nagoya, Aichi, Japan.

**RESUMEN / SUMMARY:** - Epstein-Barr virus (EBV) LMP1 is a major oncoprotein expressed in latent infection. It functions as a TNFR family member and constitutively activates cellular signals, such as NFkappaB, MAPK, JAK/STAT and AKT. We here screened small molecule inhibitors and isolated HSP90 inhibitors, Radicol and 17-AAG, as candidates that suppress LMP1 expression

and cell proliferation not only in EBV-positive SNK6 Natural Killer (NK) cell lymphoma cells, but also in B and T cells. Tumor formation in immuno-deficient NOD/Shi-scid/IL-2Rgamma(null) (NOG) mice was also retarded. These results suggest that HSP90 inhibitors can be alternative treatments for patients with EBV-positive malignancies.

[975]

**TÍTULO / TITLE:** - Interaction of CJY, an Isoflavone, with ATPase of P-glycoprotein in Doxorubicin-resistant Human Myelogenous Leukemia (K562/DOX) Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Drug Res (Stuttg). 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1055/s-0033-1345175](#)

**AUTORES / AUTHORS:** - Cen J; Liu L; He L; Ji BS

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Natural Medicine and Immune Engineering, Henan University, Kaifeng, China.

**RESUMEN / SUMMARY:** - The previous study reported CJY, an isoflavone, can reverse P-glycoprotein (P-gp)-mediated multidrug-resistance (MDR) in doxorubicin-resistant human myelogenous leukemia (K562/DOX) cells. This study will investigate the exact mechanism of CJY on P-gp. By assessment of ATPase activity, we gained further insight into the nature of the CJY interactions with P-gp. Kinetic studies on ATPase activity were applied to show the effects of Verapamil (Ver) on CJY-stimulated, CJX1 on Ver-stimulated, and CJX1 on CJY-stimulated P-gp ATPase activity. Furthermore, the combined effects of CJY with Ver, and CJY with CJX1 were also evaluated isoblographically in numerous fixed-ratio combinations of 1:1, 1:2, 1:4, 1:8, and 1:10. The results showed that basal P-gp ATPase activity was increased by CJY with half-maximal activity concentration ( $K_m$ ) of  $2.9 \pm 0.3 \mu\text{M}$  and the maximal ATPase activity velocity ( $V_{max}$ ) of  $265 \pm 21 \text{ nM} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$ . Kinetic studies on ATPase activity showed the effects of Verapamil (Ver) on CJY-stimulated, CJX1 on Ver-stimulated, and CJX1 on CJY-stimulated P-gp ATPase activity were all non-competitive inhibition, indicating that these substrates can simultaneously but independently bind to diverse sites on P-gp. The combined effects of CJY with Ver, and CJY with CJX1 show that mixtures of both drugs at these fixed-ratios displayed synergistic interactions. CJY, CJX1 and Ver bind P-gp on different sites. CJY could be applied combining with other P-gp inhibitors to get better reversal of multidrug resistance than it used alone.

[976]

**TÍTULO / TITLE:** - Evaluation of the clinical benefits of nanoparticle albumin-bound paclitaxel in women with metastatic breast cancer in British Columbia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Oncol. 2013 Apr;20(2):97-103. doi: 10.3747/co.20.1256.

●●Enlace al texto completo (gratis o de pago) [3747/co.20.1256](#)

**AUTORES / AUTHORS:** - Lohmann AE; Speers CH; Chia SK

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, BC Cancer Agency, Vancouver, BC.

**RESUMEN / SUMMARY:** - BACKGROUND: Altered formulations of taxanes may lack cross-resistance with standardly used solvent-based taxanes. The primary objective of the present study was to assess the clinical benefit of nanoparticle albumin-bound (nab)-paclitaxel in women with metastatic breast cancer previously treated with and without adjuvant taxane in British Columbia. METHODS: The BC Cancer Agency Pharmacy data repository and Breast Cancer Outcomes Unit database were linked to identify all patients who received nab-paclitaxel in British Columbia since its introduction in 2007. Hormone receptor status, demographic characteristics, number of cycles prescribed, and time to treatment failure were extracted and analyzed. RESULTS: From 2007 to 2011, 138 patients in British Columbia received nab-paclitaxel, with 122 patients available for analysis. Most (70.5%) received adjuvant chemotherapy; about a quarter (24.6%) received an adjuvant taxane. Patients who received adjuvant taxane were more likely to have node-positive (86.7% vs. 48.9%,  $p = 0.007$ ), estrogen receptor-negative (46.7% vs. 13.0%  $p < 0.001$ ) disease and to receive initial adjuvant radiotherapy (76.7% vs. 51.1%,  $p < 0.001$ ). For the entire cohort, the median number of nab-paclitaxel cycles prescribed was 4.4 (range: 0.3-13). The median number of nab-paclitaxel cycles was greater when that agent was given as first- or second-line therapy than as third-line or greater therapy (5.0 cycles vs. 3.7 cycles respectively). The median time to treatment failure was 96 days in the prior adjuvant taxane group (range: 0-361) and 73.5 days in the no prior adjuvant taxane group (range: 0-1176). CONCLUSIONS: This retrospective study demonstrates potential clinical activity of nab-paclitaxel in metastatic breast cancer regardless of whether patients had prior exposure to adjuvant taxanes.

[977]

**TÍTULO / TITLE:** - Ezrin dephosphorylation/downregulation contributes to ursolic acid-mediated cell death in human leukemia cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood Cancer J. 2013 Apr 12;3:e108. doi: 10.1038/bcj.2013.7.

●●Enlace al texto completo (gratis o de pago) [1038/bcj.2013.7](#)

**AUTORES / AUTHORS:** - Li G; Zhou T; Liu L; Chen J; Zhao Z; Peng Y; Li P; Gao N

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacognosy, College of Pharmacy, 3<sup>rd</sup> Military Medical University, Chongqing, China.

**RESUMEN / SUMMARY:** - Ezrin links the actin filaments with the cell membrane and has a functional role in the apoptotic process. It appears clear that ezrin is directly associated with Fas, leading to activation of caspase cascade and cell

death. However, the exact role of ezrin in ursolic acid (UA)-induced apoptosis remains unclear. In this study, we show for the first time that UA induces apoptosis in both transformed and primary leukemia cells through dephosphorylation/downregulation of ezrin, association and polarized colocalization of Fas and ezrin, as well as formation of death-inducing signaling complex. These events are dependent on Rho-ROCK1 signaling pathway. Knockdown of ezrin enhanced cell death mediated by UA, whereas overexpression of ezrin attenuated UA-induced apoptosis. Our in vivo study also showed that UA-mediated inhibition of tumor growth of mouse leukemia xenograft model is in association with the dephosphorylation/downregulation of ezrin. Such findings suggest that the cytoskeletal protein ezrin may represent an attractive target for UA-mediated lethality in human leukemia cells.

[978]

**TÍTULO / TITLE:** - Melatonin Suppresses the Expression of 45S Preribosomal RNA and Upstream Binding Factor and Enhances the Antitumor Activity of Puromycin in MDA-MB-231 Breast Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med.

2013;2013:879746. doi: 10.1155/2013/879746. Epub 2013 Apr 7.

●●Enlace al texto completo (gratis o de pago) [1155/2013/879746](#)

**AUTORES / AUTHORS:** - Jung JH; Sohn EJ; Shin EA; Lee D; Kim B; Jung DB; Kim JH; Yun M; Lee HJ; Park YK; Kim SH

**INSTITUCIÓN / INSTITUTION:** - College of Oriental Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea.

**RESUMEN / SUMMARY:** - Since the dysregulation of ribosome biogenesis is closely associated with tumor progression, in the current study, the critical role of ribosome biogenesis related signaling was investigated in melatonin and/or puromycin induced apoptosis in MDA-MB-231 breast cancer cells. Despite its weak cytotoxicity, melatonin from 3 mM attenuated the expression of 45S pre-ribosomal RNA (pre-rRNA), UBF as a nucleolar transcription factor, and fibrillarin at mRNA level and consistently downregulated nucleolar proteins such as UBF and fibrillarin at protein level in MDA-MB-231 cells. Furthermore, immunofluorescence assay revealed that UBF was also degraded by melatonin in MDA-MB-231 cells. In contrast, melatonin attenuated the expression of survival genes such as Bcl-xL, Mcl-1, cyclinD1, and cyclin E, suppressed the phosphorylation of AKT, mTOR, and STAT3, and cleaved PARP and activated caspase 3 only at a high concentration of 12 mM. However, combined treatment of melatonin (3 mM) and puromycin (1 μM) synergistically inhibited viability, attenuated the expression of 45S pre-rRNA and UBF, and consistently downregulated UBF, XPO1 and IPO7, procaspase 3, and Bcl-xL in MDA-MB 231 cells. Overall, these findings suggest that melatonin can be a cancer preventive agent by combination with puromycin via the inhibition of 45S pre-rRNA and UBF in MDA-MB 231 breast cancer cells.

[979]

**TÍTULO / TITLE:** - Role of insulin-like growth factor binding protein-3 in 1, 25-dihydroxyvitamin-d<sub>3</sub>-induced breast cancer cell apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Cell Biol. 2013;2013:960378. doi: 10.1155/2013/960378. Epub 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago) [1155/2013/960378](#)

**AUTORES / AUTHORS:** - Brosseau C; Pirianov G; Colston KW

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Sciences, St George's University of London, London SW17 0RE, UK.

**RESUMEN / SUMMARY:** - Insulin-like growth factor I (IGF-I) is implicated in breast cancer development and 1, 25-dihydroxyvitamin D<sub>3</sub> (1, 25-D<sub>3</sub>) has been shown to attenuate pro-survival effects of IGF-I on breast cancer cells. In this study the role of IGF binding protein-3 (IGFBP-3) in 1, 25-D<sub>3</sub>-induced apoptosis was investigated using parental MCF-7 breast cancer cells and MCF-7/VD® cells, which are resistant to the growth inhibitory effects of 1, 25-D<sub>3</sub>. Treatment with 1, 25-D<sub>3</sub> increased IGFBP-3 mRNA expression in both cell lines but increases in intracellular IGFBP-3 protein and its secretion were observed only in MCF-7. 1, 25-D<sub>3</sub>-induced apoptosis was not associated with activation of any caspase but PARP-1 cleavage was detected in parental cells. IGFBP-3 treatment alone produced cleavage of caspases 7, 8, and 9 and PARP-1 in MCF-7 cells. IGFBP-3 failed to activate caspases in MCF-7/VD® cells; however PARP-1 cleavage was detected. 1, 25-D<sub>3</sub> treatment inhibited IGF-I/Akt survival signalling in MCF-7 but not in MCF-7/VD® cells. In contrast, IGFBP-3 treatment was effective in inhibiting IGF-I/Akt pathways in both breast cancer lines. These results suggest a role for IGFBP-3 in 1, 25-D<sub>3</sub> apoptotic signalling and that impaired secretion of IGFBP-3 may be involved in acquired resistance to vitamin D in breast cancer.

[980]

**TÍTULO / TITLE:** - Phenethyl isothiocyanate inhibits androgen receptor-regulated transcriptional activity in prostate cancer cells through suppressing PCAF.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Nutr Food Res. 2013 May 10. doi: 10.1002/mnfr.201200810.

●●Enlace al texto completo (gratis o de pago) [1002/mnfr.201200810](#)

**AUTORES / AUTHORS:** - Yu C; Gong AY; Chen D; Solelo Leon D; Young CY; Chen XM

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Microbiology and Immunology, Creighton University Medical Center, Omaha, NE, USA; Department of Clinical Nursing, School of Nursing, Beijing University of Chinese Medicine, Beijing, P. R. China.

**RESUMEN / SUMMARY:** - SCOPE: Androgen receptor (AR) signaling is critical for all aspects of prostate growth and tumorigenesis. The glucosinolate-derived phenethyl isothiocyanate (PEITC) has recently been demonstrated to reduce the risk of prostate cancer (PCa) and inhibit PCa cell growth. We previously reported that p300/CBP-associated factor (PCAF), a co-regulator for AR, is upregulated in PCa cells through suppression of the mir-17 gene. Here, we assessed the effects of PEITC on PCAF expression and AR-regulated transcriptional activity in PCa cells. **METHODS AND RESULTS:** Using AR-responsive LNCaP cells, we observed the inhibitory effects of PEITC on the dihydrotestosterone-stimulated AR transcriptional activity and cell growth of PCa cells. Interestingly, overexpression of PCAF attenuated the inhibitory effects of PEITC on dihydrotestosterone-stimulated AR transcriptional activity. Expression of PCAF was upregulated in PCa cells through suppression of miR-17. PEITC treatment significantly decreased PCAF expression and promoted transcription of miR-17 in LNCaP cells. Functional inhibition of miR-17 attenuated the suppression of PCAF in cells treated by PEITC. **CONCLUSION:** Our results indicate that PEITC inhibits AR-regulated transcriptional activity and cell growth of PCa cells through miR-17-mediated suppression of PCAF, suggesting a new mechanism by which PEITC modulates PCa cell growth.

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[981]

**TÍTULO / TITLE:** - Antihyperglycemic Drug *Gymnema sylvestre* Also Shows Anticancer Potentials in Human Melanoma A375 Cells via Reactive Oxygen Species Generation and Mitochondria-Dependent Caspase Pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Integr Cancer Ther. 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago)

[1177/1534735413485419](http://1177/1534735413485419)

**AUTORES / AUTHORS:** - Chakraborty D; Ghosh S; Bishayee K; Mukherjee A; Sikdar S; Khuda-Bukhsh AR

**INSTITUCIÓN / INSTITUTION:** - University of Kalyani, Kalyani, India.

**RESUMEN / SUMMARY:** - Objective. Ethanolic extract of *Gymnema sylvestre* (GS) leaves is used as a potent antidiabetic drug in various systems of alternative medicine, including homeopathy. The present study was aimed at examining if GS also had anticancer potentials, and if it had, to elucidate its possible mechanism of action. **METHODS:** We initially tested possible anticancer potential of GS on A375 cells (human skin melanoma) through MTT assay and determined cytotoxicity levels in A375 and normal liver cells; we then thoroughly studied its apoptotic effects on A375 cells through protocols such as Hoechst 33258, H2DCFDA, and rhodamine 123 staining and conducted ELISA for cytochrome c, caspase 3, and PARP activity levels; we determined the mRNA level expression of cytochrome c, caspase 3, Bcl2, Bax, PARP, ICAD, and EGFR signaling genes through semiquantitative reverse transcriptase polymerase chain reaction and conducted Western blot analysis of caspase 3

and PARP. We also analyzed cell cycle events, determined reactive oxygen species accumulation, measured annexin V-FITC/PI and rhodamine 123 intensity by flow cytometry. RESULTS: Compared with both normal liver cells and drug-untreated A375, the mortality of GS-treated A375 cells increased in a dose-dependent manner. Additionally, GS induced nuclear DNA fragmentation and showed an increased level of mRNA expression of apoptotic signal related genes cytochrome c, caspase 3, PARP, Bax, and reduced expression level of ICAD, EGFR, and the anti-apoptotic gene Bcl2. CONCLUSION: Overall results indicate GS to have significant anticancer effect on A375 cells apart from its reported antidiabetic effect, indicating possibility of its palliative use in patients with symptoms of both the diseases.

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[982]

**TÍTULO / TITLE:** - Prophylactic use of granulocyte colony-stimulating factor after consolidation therapy with high-dose cytarabine for acute myeloid leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Rev Hematol. 2013 Apr;6(2):131-3. doi: 10.1586/ehm.13.10.

●●Enlace al texto completo (gratis o de pago) [1586/ehm.13.10](#)

**AUTORES / AUTHORS:** - Shadman M; Estey EH

**INSTITUCIÓN / INSTITUTION:** - Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA 98109, USA. [mshadman@fhcrc.org](mailto:mshadman@fhcrc.org)

**RESUMEN / SUMMARY:** - Prophylactic use of granulocyte colony-stimulating factor after chemotherapy in acute myeloid leukemia patients has become part of the supportive care strategy in some institutions. Despite shortening the neutropenia period and lowering the hospitalization rate, randomized studies have not shown any improvement in the clinical outcomes with this intervention. In their single-institution retrospective study, Bradley et al. reported that granulocyte colony-stimulating factor administration following consolidation therapy with high-dose cytarabine is associated with decreased hospitalization rate and improved survival. This finding is not consistent with the prior knowledge from the randomized studies. Herein, we review some of the explanations for the findings and re-emphasize the limitations of nonrandomized studies in assessing acute myeloid leukemia outcomes, as appreciated by the authors.

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[983]

**TÍTULO / TITLE:** - Increased placenta growth factor mRNA level is significantly associated with progression, recurrence and poor prognosis of oral squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Formos Med Assoc. 2013 May;112(5):253-8. doi: 10.1016/j.jfma.2012.04.009. Epub 2012 Aug 3.

●●Enlace al texto completo (gratis o de pago) [1016/j.jfma.2012.04.009](#)

**AUTORES / AUTHORS:** - Cheng SJ; Cheng SL; Lee JJ; Chen HM; Chang HH; Kok SH; Chiang ML; Kuo MY

**INSTITUCIÓN / INSTITUTION:** - Graduate Institute of Clinical Dentistry, National Taiwan University, Taipei, Taiwan; School of Dentistry, National Taiwan University, Taipei, Taiwan; Department of Dentistry, National Taiwan University Hospital, College of Medicine, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - **BACKGROUND/PURPOSE:** Expression of placenta growth factor (PIGF) mRNA is shown to correlate with the progression and prognosis of several human cancers. In this study, we assessed whether the PIGF mRNA level in oral squamous cell carcinoma (OSCC) tissue could be used to predict the progression and prognosis of OSCCs in Taiwan. **METHODS:** This study used quantitative real-time reverse transcription-polymerase chain reaction (quantitative RT-PCR) to detect the PIGF mRNA levels in 63 paired OSCC and adjacent normal-looking oral mucosa (non-OSCC) tissues. Threshold cycle (CT) was defined as the PCR cycle number needed to generate a pre-determined amount of DNA (threshold). For a chosen threshold, a smaller starting copy number of mRNA results in a higher CT value. In this study, the relative expression level of tissue PIGF mRNA in each OSCC patients was expressed as  $-\Delta\text{CT} = -(\text{OSCC CT} - \text{non-OSCC CT})$ . Thus, the higher the  $-\Delta\text{CT}$ , the greater the copy number of PIGF mRNA in tissues. **RESULTS:** We found that the higher mean PIGF mRNA  $-\Delta\text{CT}$  value was significantly associated with OSCCs with larger tumor size ( $p = 0.03$ ), positive lymph node metastasis ( $p = 0.003$ ), more advanced clinical stages ( $p = 0.013$ ) or the presence of loco-regional recurrence ( $p = 0.039$ ). Positive lymph node metastasis ( $p = 0.019$ ) and PIGF mRNA  $-\Delta\text{CT}$  value  $>2$  ( $p = 0.016$ ) were identified as two independent unfavorable prognosis factors by multivariate analyses with Cox regression model. Moreover, Kaplan-Meier curve showed that OSCC patients with a PIGF mRNA  $-\Delta\text{CT}$  value  $>2$  had a significantly poorer recurrence-free survival than those with a PIGF mRNA  $-\Delta\text{CT}$  value  $\leq 2$  (log-rank test,  $p = 0.017$ ). **CONCLUSION:** The OSCC tissue PIGF mRNA level can be used to predict the progression and prognosis of OSCCs in Taiwan.

[984]

**TÍTULO / TITLE:** - Expression of E-cadherin and KRAS mutation may serve as biomarkers of cetuximab-based therapy in metastatic colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1295-1300. Epub 2013 Feb 8.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1187](#)

**AUTORES / AUTHORS:** - Nakamoto K; Nagahara H; Maeda K; Noda E; Inoue T; Yashiro M; Nishiguchi Y; Ohira M; Hirakawa K

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan.

**RESUMEN / SUMMARY:** - Cetuximab (Cmab), a chimeric monoclonal antibody for targeting the epidermal growth factor receptor, has become one of the standard treatments for metastatic colorectal cancer (mCRC). However, only a small proportion of patients respond to Cmab, and it has been reported that KRAS mutation is a negative biomarker of response to Cmab therapy. The aim of this study was to detect additional biomarkers of response to Cmab therapy in patients with mCRC. We evaluated the effects of Cmab therapy in 36 patients with mCRC according to the Response Evaluation Criteria in Solid Tumors, and classified patients who achieved complete response, partial response or stable disease as responders, and patients who achieved progressive disease as non-responders. We retrospectively examined the difference between the two groups using KRAS analysis and immunohistochemistry to determine the expression of E-cadherin, p53 and Ki67. Nineteen patients were responders, while 17 patients were non-responders. KRAS status and expression of E-cadherin were significantly correlated with the effect of Cmab therapy. Moreover, the expression of E-cadherin was significantly correlated with the effect of Cmab therapy in KRAS wild-type patients. In KRAS mutant-type patients, the expression of E-cadherin did not significantly correlate with the effect of Cmab therapy, but all responders with KRAS mutant-type tumors expressed E-cadherin. Our results indicate that the expression of E-cadherin detected by immunohistochemistry may be a positive predictor of Cmab-based therapy in mCRC, and that a combination of E-cadherin immunohistochemistry and KRAS analysis may be a more sensitive biomarker than KRAS analysis alone.

[985]

**TÍTULO / TITLE:** - High-Dose Cytarabine (HD araC) in the Treatment of Leukemias: a Review.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Hematol Malig Rep. 2013 Jun;8(2):141-8. doi: 10.1007/s11899-013-0156-3.

●●Enlace al texto completo (gratis o de pago) [1007/s11899-013-0156-](#)

[3](#)

**AUTORES / AUTHORS:** - Reese ND; Schiller GJ

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, David Geffen School of Medicine at UCLA, 757 Westwood Plaza, Suite 7501, Los Angeles, CA, 90095, USA, [nreese@mednet.ucla.edu](mailto:nreese@mednet.ucla.edu).

**RESUMEN / SUMMARY:** - Cytarabine (araC) has served as the backbone of acute myeloid leukemia (AML) treatment for nearly forty years. High-dose cytarabine (HD araC) therapy resulted from a theoretical model developed in the 1970s that attempted to maximize the anti-leukemia effect of cytarabine. Since that time, HD araC has been utilized mostly in consolidation therapy for AML and in patients with relapsed or resistant AML. The development of araC and HD araC preceded our current understanding of AML biology-that it is a heterogeneous

disease, not a single clinical entity. Thus, the optimal dose, schedule, and clinical setting for the use of cytarabine in hematologic malignancies remain uncertain. Research is now better defining the optimal use of HD araC based on leukemia cell karyotype and molecular signature. Here we review the pharmacodynamics of araC, the landmark studies that established the role of HD araC in AML, and research defining the role of HD araC based on the unique biologic properties of the leukemia cell.

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[986]

**TÍTULO / TITLE:** - Enhanced levels of the apoptotic BAX/BCL-2 ratio in children with acute lymphoblastic leukemia and high-risk features.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Biol. 2013 Mar;36(1):7-11. doi: 10.1590/S1415-47572013005000003. Epub 2013 Mar 4.

●●Enlace al texto completo (gratis o de pago) [1590/S1415-47572013005000003](#)

**AUTORES / AUTHORS:** - Kaparou M; Choumerianou D; Perdikogianni C; Martimianaki G; Kalmanti M; Stiakaki E

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Hematology-Oncology, University Hospital of Heraklion, Heraklion, Crete, Greece.

**RESUMEN / SUMMARY:** - It has been suggested that leukemia is characterized by an impaired balance between the proliferation of blood cells and their capacity to undergo apoptosis. The aim of this study was to examine the expression of key molecules related to apoptosis (BCL-2, BAX, FAS, FAS-L) in children with acute lymphoblastic leukemia (ALL). Measurement of BCL-2 and BAX mRNA was performed by quantitative real-time PCR, and membrane expression of FAS and FAS-L was assessed by flow cytometry in bone marrow mononuclear cells, both at diagnosis and at remission following induction chemotherapy. At diagnosis, increased levels of the apoptotic BAX/BCL-2 ratio were observed in children older than 10 years and with higher white blood cell counts. A DNA index < 1.16 was associated with increased BAX/BCL-2, both at diagnosis and at remission, and the del(9p) chromosome abnormality with increased BAX/BCL-2 at remission. The expression of the apoptotic receptor FAS was significantly higher at remission compared to diagnosis, which might reflect enhanced sensitivity of the leukemic clone to apoptosis and response to treatment. Altogether, our results highlight the association of apoptosis-related genes with clinical and cytogenetic prognostic parameters in pediatric ALL. A better understanding of the mechanisms and regulation of apoptosis should enable the design of novel targeted therapies for these patients.

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[987]

**TÍTULO / TITLE:** - Cholesterol dependent uptake and interaction of Doxorubicin in mcf-7 breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Sci. 2013 Apr 16;14(4):8358-66. doi: 10.3390/ijms14048358.

●●Enlace al texto completo (gratis o de pago) [3390/ijms14048358](https://doi.org/10.3390/ijms14048358)

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**RESUMEN / SUMMARY:** - Methods of fluorescence spectroscopy and microscopy-including intensity and lifetime (FLIM) images-are used to examine uptake, intracellular location and interaction of the chemotherapeutic drug doxorubicin in MCF-7 human breast cancer cells as a function of cholesterol content. By comparing cells with natural and decreased cholesterol levels after 2 h or 24 h incubation with doxorubicin, we observed that higher fluorescence intensities and possibly shortened fluorescence lifetimes-reflecting increased uptake of the drug and more pronounced drug response-are concomitant with higher membrane fluidity.

[988]

**TÍTULO / TITLE:** - Gene expression profiling in breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Transl Res. 2013;5(2):132-8. Epub 2013 Mar 28.

**AUTORES / AUTHORS:** - Arango BA; Rivera CL; Gluck S

**INSTITUCIÓN / INSTITUTION:** - University of Miami/Sylvester Comprehensive Cancer Center Miami, FL, USA.

**RESUMEN / SUMMARY:** - In recent years, molecular research has translated into remarkable changes of breast cancer diagnostics and therapeutics. Molecular tests such as the 21 gene expression test (Oncotype DX™) and 70 gene microarray test (MammaPrint®) have revolutionized the predictive and prognostic tools in the clinic. By stratifying the risk of recurrence for patients, the tests are able to provide clinicians with more information on the treatment outcomes of using chemotherapy, HER2 targeted therapy or endocrine therapy or the combination of the therapies for patients with particular genetic expressions. However, it is still questionable for clinical applications as some areas remain unclear and that the true benefit still needs prospective evaluation. Such studies are under way and are anxiously awaited. In this paper, the limitation of the molecular tests are discussed. As we are moving towards personalized medicine, molecular profiling will not only result in better outcomes but in a certain proportion of patients, likely will spare unnecessary use of cytotoxic compounds and reduce the cost to the health care systems.

[989]

**TÍTULO / TITLE:** - Effect of IL-18 gene promoter polymorphisms on prostate cancer occurrence and prognosis in Han Chinese population.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Res. 2013 Mar 15;12(1):820-9. doi: 10.4238/2013.March.15.2.

●●Enlace al texto completo (gratis o de pago) [4238/2013.March.15.2](https://doi.org/10.4238/2013.March.15.2)

**AUTORES / AUTHORS:** - Liu JM; Liu JN; Wei MT; He YZ; Zhou Y; Song XB; Ying BW; Huang J

**INSTITUCIÓN / INSTITUTION:** - Department of Urology Surgery, West China School of Medicine, West China Hospital, Sichuan University, Sichuan Province, P.R. China.

**RESUMEN / SUMMARY:** - Interleukin-18 (IL-18) has been implicated in a wide variety of cellular functions that affect the biological response to tumors. However, there is insufficient evidence to prove that IL-18 gene variants are associated with risk of prostate cancer. We examined a possible association between two promoter polymorphisms, -137G/C (rs187238) and -607C/A (rs1946518), in the IL-18 gene and prostate cancer occurrence and prognosis in Han Chinese. We used a high-resolution melting method to genotype these two polymorphisms in 375 Chinese Han patients with prostate cancer and in 400 age-matched healthy controls. A hundred and eighty-one prostate cancer patients who had been receiving androgen deprivation therapy, including operational and medical castration, were enrolled to follow-up in this study. Carriers of the GG genotype of the -137G/C polymorphism had a 2.165-times higher risk of prostate cancer progression than carriers of GC [95% confidence interval (CI) = 1.270-3.687]. Patients with the GG genotype at clinical stages III and IV also had significantly lower rates of progression-free survival (relative risk = 2.174, 95%CI = 1.211-3.906). However, we found no significant association of genotype or allele distributions of these two polymorphisms with occurrence of prostate cancer. We conclude that there is evidence that the IL-18 gene promoter polymorphism -137G/C influences the prognosis of prostate cancer patients in androgen deprivation therapy, although neither of the two SNPs contributes to prostate cancer development.

[990]

**TÍTULO / TITLE:** - A case of pancreatic neuroendocrine tumor with excessively-advanced liver metastasis treated with S-1/GEM combination chemotherapy plus the long-acting somatostatin analogue octreotide.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nihon Shokakibyō Gakkai Zasshi. 2013 Apr;110(4):660-8.

**AUTORES / AUTHORS:** - Yoshida Y; Sugawara N; Minami T; Iwata N; Ikeda K; Endoh T; Sasano H

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Sapporo Dohto Hospital.

**RESUMEN / SUMMARY:** - A 41-year-old woman who had a pancreatic tail tumor and multiple liver tumors was referred to our hospital. The results of abdominal US, CT and MRI, and histopathological and immunohistochemical findings of the liver tumor biopsy revealed a pancreatic neuroendocrine tumor with

excessively-advanced liver metastasis. We treated her with S-1/gemcitabine combination chemotherapy plus long-acting somatostatin analogue octreotide, which produced tumor stabilization and good quality of life for 7 months, and survival time of 15 months. Although the tumor was diagnosed as a poorly differentiated endocrine carcinoma, this therapy was suggested to be effective in this case.

[991]

**TÍTULO / TITLE:** - Knockdown of TRB3 induces apoptosis in human lung adenocarcinoma cells through regulation of Notch 1 expression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jul;8(1):47-52. doi: 10.3892/mmr.2013.1453. Epub 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1453](#)

**AUTORES / AUTHORS:** - Zhou H; Luo Y; Chen JH; Hu J; Luo YZ; Wang W; Zeng Y; Xiao L

**INSTITUCIÓN / INSTITUTION:** - Tumor Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan 410013, P.R. China.

**RESUMEN / SUMMARY:** - The upregulation of tribbles homolog 3 (TRB3), a pseudokinase in mammals, has been observed in several types of malignant cancer, including thyroid, ovarian, liver and colorectal cancer. However, the pathological role and the regulatory mechanism of TRB3 in cancer remain unknown. In the current study, we demonstrated that the expression of TRB3 was upregulated in non-small cell lung cancer (NSCLC), correlating with tumor metastasis, disease recurrence and poor survival in patients. Knocking down TRB3 in aggressive lung cancer cell lines was demonstrated to significantly inhibit their malignant behaviors, including in vitro invasion and cell proliferation, as well as in vivo metastasis and tumor growth. The correlation between TRB3 and Notch 1 expression revealed that Notch 1 was downregulated by the knockdown of TRB3 in the lung adenocarcinoma cell lines. These results have provided insights into the correlation between TRB3 expression and lung cancer progression, and thus may have potential for the prognosis and therapy of lung cancer.

[992]

**TÍTULO / TITLE:** - Mechanisms of apple polyphenols-induced proliferation inhibiting and apoptosis in a metastatic oral adenoid cystic carcinoma cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Kaohsiung J Med Sci. 2013 May;29(5):239-45. doi: 10.1016/j.kjms.2012.09.001. Epub 2012 Dec 21.

●●Enlace al texto completo (gratis o de pago) [1016/j.kjms.2012.09.001](#)

**AUTORES / AUTHORS:** - Zheng CQ; Qiao B; Wang M; Tao Q

**INSTITUCIÓN / INSTITUTION:** - Guanghua School and Hospital of Stomatology and Institute of Stomatological Research, Sun Yat-sen University, Guangzhou, Guangdong Province, China.

**RESUMEN / SUMMARY:** - Adenoid cystic carcinoma (ACC) is characterized by intensive local invasion and high incidence of distant metastases. Conventional chemotherapy for ACC produces a poor result. We aimed to evaluate the effect of apple polyphenols (APs), a novel nutraceutical agent, on the proliferation and apoptosis levels in a metastatic oral ACC cell line. A metastatic ACC (ACC-M) cell line and control cells (MRC-5 cells derived from normal lung tissue) were treated with APs at different concentrations. MTT assay was used to determine the in vitro cytotoxicity. The cell cycle distribution and apoptosis levels were measured by flow cytometry. To evaluate the mechanism of APs, vascular endothelial growth factor receptor-2 (VEGFR-2) and caspase-3 messenger ribonucleic acid (mRNA) and protein levels were evaluated by reverse transcription-polymerase chain reaction and Western blots, respectively. After cells were cultured for 24 hours or 48 hours, the critical concentration of cytotoxicity of APs in MRC-5 cells was found to be 250 µg/mL. In contrast, in the concentration range of 100-250 µg/mL, the cytotoxicity of APs in ACC-M cells was time- and dose-dependent: ACC-M cell proliferation declined at 100 µg/mL when cultured for 48 hours, whereas growth was not inhibited at the concentrations of APs below 200 µg/mL when cultured for 24 hours. In selected time and dose patterns (ACC-M cells cultured at the concentrations of 150 and 250 µg/mL for 48 hours), the flow cytometry performance showed that apoptosis and necrosis occurred in APs-treated ACC-M cells. Also, in these patterns, VEGFR-2 mRNA and protein levels decreased whereas the levels of caspase-3 increased. In summary, APs could inhibit proliferation and induce apoptosis in ACC-M cells in vitro. These effects may be related to the downregulation of VEGFR-2 expression and the activation of caspase-3 expression.

[993]

**TÍTULO / TITLE:** - Protein phosphatase magnesium-dependent 1delta (PPM1D) mRNA expression is a prognosis marker for hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e60775. doi: 10.1371/journal.pone.0060775. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060775](http://1371/journal.pone.0060775)

**AUTORES / AUTHORS:** - Li GB; Zhang XL; Yuan L; Jiao QQ; Liu DJ; Liu J

**INSTITUCIÓN / INSTITUTION:** - Department of Liver Transplantation and Hepatobiliary Surgery, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, People's Republic of China.

**RESUMEN / SUMMARY:** - BACKGROUND: Protein phosphatase magnesium-dependent 1delta (PPM1D) is an oncogene, overexpressed in many solid tumors, including ovarian cancer and breast cancer. The current study examined the expression and the prognostic value of PPM1D mRNA in human hepatocellular carcinoma (HCC). METHODS: Total RNA was extracted from 86 HCC and paired non-cancerous liver tissues. PPM1D mRNA expression was determined by real-time quantitative reverse transcriptase-polymerase chain reaction (qPCR). Immunohistochemistry assay was used to verify the expression of ppm1d protein in the HCC and non-cancerous liver tissues. HCC patients were grouped according to PPM1D mRNA expression with the average PPM1D mRNA level in non-cancerous liver tissue samples as the cut-off. Correlations between clinicopathologic variables, overall survival and PPM1D mRNA expression were analyzed. FINDINGS: PPM1D mRNA was significantly higher in HCC than in the paired non-cancerous tissue ( $p < 0.01$ ). This was confirmed by ppm1d staining. 56 patients were classified as high expression group and the other 30 patients were categorized as low expression group. There were significant differences between the two groups in term of alpha-fetoprotein (alpha-FP) level ( $p < 0.01$ ), tumor size ( $p < 0.01$ ), TNM stage ( $p < 0.01$ ), recurrence incidence ( $p < 0.01$ ) and family history of liver cancer ( $p < 0.01$ ). The current study failed to find significant differences between the two groups in the following clinical characteristics: age, gender, portal vein invasion, lymphnode metastasis, hepatitis B virus (HBV) infection and alcohol intake. Survival time of high expression group was significantly shorter than that of low expression group (median survival, 13 months and 32 months, respectively,  $p < 0.01$ ). CONCLUSION: Up-regulation of PPM1D mRNA was associated with progressive pathological feature and poor prognosis in HCC patients. PPM1D mRNA may serve as a prognostic marker in HCC.

[994]

**TÍTULO / TITLE:** - In Vitro and In Vivo Evaluation of the Caspase-3 Substrate-Based Radiotracer [F]-CP18 for PET Imaging of Apoptosis in Tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Imaging Biol. 2013 May 21.

●●Enlace al texto completo (gratis o de pago) [1007/s11307-013-0646-](#)

[7](#)

**AUTORES / AUTHORS:** - Xia CF; Chen G; Gangadharmath U; Gomez LF; Liang Q; Mu F; Mocharla VP; Su H; Szardenings AK; Walsh JC; Zhao T; Kolb HC

**INSTITUCIÓN / INSTITUTION:** - Molecular Imaging Biomarker Research, Siemens Medical Solutions USA, Inc., 6100 Bristol Parkway, Culver City, CA, 90230, USA.

**RESUMEN / SUMMARY:** - PURPOSE: A novel caspase-3 substrate-based probe [18F]-CP18 was evaluated as an in vivo positron emission tomography (PET) imaging agent for monitoring apoptosis in tumors. METHODS: Uptake of [18F]-CP18 in cell assays and tumors was measured. Caspase-3/7 activities in cell

lysates and tumor homogenates were determined. Autoradiography, Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), and cleaved caspase-3 immunostaining were performed on adjacent tumor sections to identify areas of apoptosis. RESULTS: The in vitro cell assays showed caspase-3-dependent uptake of [18F]-CP18 in tumor cells when treated with an apoptosis inducer. The in vivo microPET imaging signal of [18F]-CP18 in xenograft tumors correlated with the ex vivo caspase-3/7 activities in these tumors. Furthermore, tumor autoradiographies of [18F]-CP18 in tumor sections matched adjacent sections stained by TUNEL and caspase-3 immunohistochemistry (IHC). CONCLUSIONS: [18F]-CP18 demonstrated high affinity and selectivity for activated caspase-3 both in vitro and in vivo, and the results support [18F]-CP18 as a promising new PET imaging agent for apoptosis.

[995]

**TÍTULO / TITLE:** - Effect of autophagy inhibition on chemotherapy-induced apoptosis in A549 lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1261-1265. Epub 2013 Jan 25.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1154](#)

**AUTORES / AUTHORS:** - Liu F; Liu D; Yang Y; Zhao S

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, P.R. China.

**RESUMEN / SUMMARY:** - Chemotherapy is one of the main methods of cancer treatment and is known to induce autophagy in cancer cells. The main mechanism of chemotherapeutic agents is to promote apoptosis. In the process of chemotherapy, there is a unique association between autophagy and apoptosis. In this study, MDC staining, Hoechst 33342 staining and flow cytometry were used to explore the effects of autophagy on chemotherapy-induced apoptosis in A549 lung cancer cells and the association between autophagy and apoptosis was investigated via the addition of an autophagic inhibitor (3-methyladenine, 3-MA). This study demonstrated that cisplatin and paclitaxel were able to induce autophagy and apoptosis in A549 lung cancer cells and the inhibition of autophagy promoted cisplatin and paclitaxel-induced apoptosis. Furthermore, autophagy may play a protective role in the processes of cisplatin and paclitaxel-induced apoptosis.

[996]

**TÍTULO / TITLE:** - Honokiol Eliminates Human Oral Cancer Stem-Like Cells Accompanied with Suppression of Wnt/ beta -Catenin Signaling and Apoptosis Induction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:146136. doi: 10.1155/2013/146136. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [1155/2013/146136](https://doi.org/10.1155/2013/146136)

**AUTORES / AUTHORS:** - Yao CJ; Lai GM; Yeh CT; Lai MT; Shih PH; Chao WJ; Whang-Peng J; Chuang SE; Lai TY

**INSTITUCIÓN / INSTITUTION:** - Cancer Center, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan ; Center of Excellence for Cancer Research, Taipei Medical University, Taipei 11031, Taiwan.

**RESUMEN / SUMMARY:** - Honokiol, an active compound of *Magnolia officinalis*, exerted many anticancer effects on various types of cancer cells. We explored its effects on the elimination of cancer stem-like side population (SP) cells in human oral squamous cell carcinoma SAS cells. The sorted SP cells possessed much higher expression of stemness genes, such as ABCG2, ABCC5, EpCAM, OCT-4, CD133, CD44, and beta -catenin, and more clonogenicity as compared with the Non-SP cells. After 48 h of treatment, honokiol dose dependently reduced the proportion of SP from 2.53% to 0.09%. Apoptosis of honokiol-treated SP cells was evidenced by increased annexin V staining and cleaved caspase-3 as well as decreased Survivin and Bcl-2. Mechanistically, honokiol inhibited the CD44 and Wnt/ beta -catenin signaling of SP cells. The Wnt signaling transducers such as beta -catenin and TCF-4 were decreased in honokiol-treated SP cells, while the beta -catenin degradation promoting kinase GSK-3 alpha / beta was increased. Consistently, the protein levels of beta -catenin downstream targets such as c-Myc and Cyclin D1 were also downregulated. Furthermore, the beta -catenin-related EMT markers such as Slug and Snail were markedly suppressed by honokiol. Our findings indicate honokiol may be able to eliminate oral cancer stem cells through apoptosis induction, suppression of Wnt/ beta -catenin signaling, and inhibition of EMT.

[997]

**TÍTULO / TITLE:** - p53 DNA Binding Cooperativity Is Essential for Apoptosis and Tumor Suppression In Vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Rep. 2013 May 30;3(5):1512-25. doi: 10.1016/j.celrep.2013.04.008. Epub 2013 May 9.

●●Enlace al texto completo (gratis o de pago)

[1016/j.celrep.2013.04.008](https://doi.org/10.1016/j.celrep.2013.04.008)

**AUTORES / AUTHORS:** - Timofeev O; Schlereth K; Wanzel M; Braun A; Nieswandt B; Pagenstecher A; Rosenwald A; Elsasser HP; Stiewe T

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Oncology, Philipps University, 35032 Marburg, Germany.

**RESUMEN / SUMMARY:** - Four molecules of the tumor suppressor p53 assemble to cooperatively bind proapoptotic target genes. The structural basis for cooperativity consists of interactions between adjacent DNA binding domains. Mutations at the interaction interface that compromise cooperativity were identified in cancer patients, suggesting a requirement of cooperativity for tumor suppression. We report on an analysis of cooperativity mutant p53(E177R)

mice. Apoptotic functions of p53 triggered by DNA damage and oncogenes were abolished in these mice, whereas functions in cell-cycle control, senescence, metabolism, and antioxidant defense were retained and were sufficient to suppress development of spontaneous T cell lymphoma. Cooperativity mutant mice are nevertheless highly cancer prone and susceptible to different oncogene-induced tumors. Our data underscore the relevance of DNA binding cooperativity for p53-dependent apoptosis and tumor suppression and highlight cooperativity mutations as a class of p53 mutations that result in a selective loss of apoptotic functions due to an altered quaternary structure of the p53 tetramer.

[998]

**TÍTULO / TITLE:** - Impact of an Altered Wnt1/beta-Catenin Expression on Clinicopathology and Prognosis in Clear Cell Renal Cell Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Mol Sci. 2013 May 24;14(6):10944-57. doi: 10.3390/ijms140610944.

●●Enlace al texto completo (gratis o de pago) [3390/ijms140610944](#)

**AUTORES / AUTHORS:** - Kruck S; Eylich C; Scharpf M; Sievert KD; Fend F; Stenzl A; Bedke J

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Eberhard Karls University Tuebingen, Hoppe-Seyler Strasse 3, Tuebingen 72076, Germany.

[bedke@live.com](mailto:bedke@live.com).

**RESUMEN / SUMMARY:** - In renal cell carcinoma (RCC), single members of the Wnt/beta-catenin signaling cascade were recently identified to contribute to cancer progression. However, the role of Wnt1, one of the key ligands in beta-catenin regulation, is currently unknown in RCC. Therefore, alterations of the Wnt1/beta-catenin axis in clear cell RCC (ccRCC) were examined with regard to clinicopathology, overall survival (OS) and cancer specific survival (CSS). Corresponding ccRCCs and benign renal tissue were analyzed in 278 patients for Wnt1 and beta-catenin expression by immunohistochemistry in tissue microarrays. Expression scores, including intensity and percentage of stained cells, were compared between normal kidney and ccRCCs. Data was categorized according to mean expression scores and correlated to tumor and patients' characteristics. Survival was analyzed according to the Kaplan-Meier and log-rank test. Univariable and multivariable Cox proportional hazard regression models were used to explore the independent prognostic value of Wnt1 and beta-catenin. In ccRCCs, high Wnt1 was associated with increased tumor diameter, stage and vascular invasion ( $p \leq 0.02$ ). High membranous beta-catenin was associated with advanced stage, vascular invasion and tumor necrosis ( $p \leq 0.01$ ). Higher diameter, stage, node involvement, grade, vascular invasion and sarcomatoid differentiation ( $p \leq 0.01$ ) were found in patients with high cytoplasmic beta-catenin. Patients with a high cytoplasmic beta-catenin had a significantly reduced OS (hazard ratio (HR) 1.75) and CSS

(HR 2.26), which was not independently associated with OS and CSS after adjustment in the multivariable model. Increased ccRCC aggressiveness was reflected by an altered Wnt1/beta-catenin signaling. Cytoplasmic beta-catenin was identified as the most promising candidate associated with unfavorable clinicopathology and impaired survival. Nevertheless, the shift of membranous beta-catenin to the cytoplasm with a subsequently increased nuclear expression, as shown for other malignancies, could not be demonstrated to be present in ccRCC.

[999]

**TÍTULO / TITLE:** - Valproic acid upregulates NKG2D ligand expression and enhances susceptibility of human renal carcinoma cells to NK cell-mediated cytotoxicity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Med Sci. 2013 Apr 20;9(2):323-31. doi: 10.5114/aoms.2013.34413. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [5114/aoms.2013.34413](#)

**AUTORES / AUTHORS:** - Yang F; Shao Y; Yang F; Liu M; Huang J; Zhu K; Guo C; Luo J; Li W; Yang B; Shi J; Zheng J

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Tenth People's Hospital of Tongji University, Shanghai, China.

**RESUMEN / SUMMARY:** - INTRODUCTION: We aimed to investigate the effect of valproic acid (VPA) on NKG2D ligand expression in human renal carcinoma cell lines and to investigate the mechanisms. MATERIAL AND METHODS: Different concentrations of VPA from 0.5 mM to 8.0 mM were applied to 786-O and ACHN cell lines, respectively. Cell viability after treatment with VPA was determined by flow cytometry (FCM). Real-time PCR and FCM were used to detect the changes of mRNA and protein level of NKG2D ligands (MICA/B and ULBPs) in the two cell lines treated with 4 mM VPA. The cytotoxicity assay and CD107a mobilization assay were carried out to detect the cytotoxicity changes of NK cells against renal carcinoma cell lines after the same treatment. RESULTS: Valproic acid can efficiently upregulate MICA/B, ULBP1 and ULBP2 expression in the renal carcinoma cell lines at the mRNA and protein level ( $p < 0.05$ ). 786-O and ACHN cells treated with VPA were more susceptible to killing by NK cells than untreated cells and the enhanced cytotoxicity of NK cells was blocked by the pretreatment of NK cells with anti-NKG2D monoclonal antibodies ( $p < 0.05$ ). CONCLUSIONS: Valproic acid can clearly induce the expression of NKG2D ligands of renal carcinoma cell lines, thereby enhancing the cytotoxicity of NK cells against renal carcinoma cell lines.

[1000]

**TÍTULO / TITLE:** - Three-Dimensional Collagen I Promotes Gemcitabine Resistance In Vitro in Pancreatic Cancer Cells through HMGA2-Dependent Histone Acetyltransferase Expression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 16;8(5):e64566. doi: 10.1371/journal.pone.0064566. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064566](#)

**AUTORES / AUTHORS:** - Dangi-Garimella S; Sahai V; Ebine K; Kumar K; Munshi HG

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology/Oncology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States of America.

**RESUMEN / SUMMARY:** - Pancreatic ductal adenocarcinoma (PDAC) is associated with a pronounced collagen-rich stromal reaction that has been shown to contribute to chemo-resistance. We have previously shown that PDAC cells are resistant to gemcitabine chemotherapy in the collagen microenvironment because of increased expression of the chromatin remodeling protein high mobility group A2 (HMGA2). We have now found that human PDAC tumors display higher levels of histone H3K9 and H3K27 acetylation in fibrotic regions. We show that relative to cells grown on tissue culture plastic, PDAC cells grown in three-dimensional collagen gels demonstrate increased histone H3K9 and H3K27 acetylation, along with increased expression of p300, PCAF and GCN5 histone acetyltransferases (HATs). Knocking down HMGA2 attenuates the effect of collagen on histone H3K9 and H3K27 acetylation and on collagen-induced p300, PCAF and GCN5 expression. We also show that human PDAC tumors with HMGA2 demonstrate increased histone H3K9 and H3K27 acetylation. Additionally, we show that cells in three-dimensional collagen gels demonstrate increased protection against gemcitabine. Significantly, down-regulation of HMGA2 or p300, PCAF and GCN5 HATs sensitizes the cells to gemcitabine in three-dimensional collagen. Overall, our results increase our understanding of how the collagen microenvironment contributes to chemo-resistance in vitro and identify HATs as potential therapeutic targets against this deadly cancer.

[1001]

**TÍTULO / TITLE:** - SERPINA3K induces apoptosis in human colorectal cancer cells via activating the Fas/FasL/caspase-8 signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - FEBS J. 2013 Apr 25. doi: 10.1111/febs.12303.

●●Enlace al texto completo (gratis o de pago) [1111/febs.12303](#)

**AUTORES / AUTHORS:** - Yao Y; Li L; Huang X; Gu X; Xu Z; Zhang Y; Huang L; Li S; Dai Z; Li C; Zhou T; Cai W; Yang Z; Gao G; Yang X

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China.

**RESUMEN / SUMMARY:** - SERPINA3K, also known as kallikrein-binding protein (KBP), is a serine proteinase inhibitor with anti-inflammatory and anti-

angiogenic activities. Our previous studies showed that SERPINA3K inhibited proliferation in a dose-dependent manner and induced apoptosis of endothelial cells but had no influence on SGC-7901 gastric carcinoma cells or HepG2 hepatocarcinoma cells. However, it is unknown whether SERPINA3K has a direct impact on other carcinoma cells and which mechanisms are involved. In this study, we report for the first time that SERPINA3K not only decreased cell viability but also induced apoptosis in the colorectal carcinoma cell lines SW480 and HT-29. SERPINA3K-induced apoptosis of SW480 and HT-29 was rescued by interference with Fas ligand (FasL) small hairpin RNA. Moreover, SERPINA3K increased the expression of FasL and activated caspase-8. Peroxisome proliferator-activated receptor gamma (PPARgamma), a transcription factor of FasL, was also upregulated by SERPINA3K in a dose-dependent manner. The upregulation effect of FasL induced by SERPINA3K was reversed after interference with PPARgamma small interfering RNA. These results demonstrated that SERPINA3K-induced SW480 and HT-29 cell apoptosis was mediated by the PPARgamma/Fas/FasL signaling pathway. Therefore, our study provides additional insight into the direct anti-tumor function by inducing tumor cell apoptosis of SERPINA3K in colorectal tumors.

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[1002]

**TÍTULO / TITLE:** - Synergistic Effect between Sphingosine-1-Phosphate and Chemotherapy Drugs against Human Brain-metastasized Breast Cancer MDA-MB-361 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer. 2013;4(4):315-9. doi: 10.7150/jca.5956. Epub 2013 Mar 25.

●●Enlace al texto completo (gratis o de pago) [7150/jca.5956](http://7150/jca.5956)

**AUTORES / AUTHORS:** - Sultan A; Ling B; Zhang H; Ma B; Michel D; Alcorn J; Yang J

**INSTITUCIÓN / INSTITUTION:** - 1. Drug Discovery and Development Research Group, College of Pharmacy and Nutrition, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada.

**RESUMEN / SUMMARY:** - Sphingosine-1-phosphate (S1P) is an important sphingolipid metabolite regulating key physiological and pathophysiological processes such as cell growth and survival and tumor angiogenesis. Significant research evidence links elevated cellular S1P concentration to cancer cell proliferation, migration and angiogenesis. Physiological levels of S1P are tightly regulated and maintained at the low nanomolar level. In cancer, S1P may exist well beyond the low nanomolar level. Recently, we reported that S1P selectively induces cell apoptosis of the breast cancer MCF7 cell line at concentrations higher than 1 microM and co-administration of 1 microM S1P significantly increased the cytotoxicity of chemotherapy drug docetaxel. In this study, we show that S1P caused minor increases in cell proliferation or apoptosis, in a concentration-dependent manner, yet co-administration of 10 microM S1P

exhibited a significant synergistic effect with chemotherapy drugs docetaxel, doxorubicin and cyclophosphamide. S1P increased the cytotoxic potential of each drug by 2-fold, 3-fold, and 10-fold, respectively, against the breast cancer metastatic cell line MDA-MB-361. This synergism may suggest improved anticancer drug therapy by co-administration of exogenous S1P.

[1003]

**TÍTULO / TITLE:** - Interferon-alpha sensitizes HBx-expressing hepatocarcinoma cells to chemotherapeutic drugs through inhibition of HBx-mediated NF-kappaB activation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Virol J. 2013 May 29;10(1):168.

●●Enlace al texto completo (gratis o de pago) [1186/1743-422X-10-168](#)

**AUTORES / AUTHORS:** - Liu Y; Lou G; Wu W; Shi Y; Zheng M; Chen Z

**RESUMEN / SUMMARY:** - BACKGROUND: Hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) is characterized by high chemotherapy resistance; however, the underlying mechanism has not been fully clarified. In addition, HBx protein has been reported to play a key role in virus-mediated hepatocarcinogenesis. Therefore, the present study aims to investigate the role of HBx in the drug-resistance of METHODS: We established HBx-expressing cells by liposome-mediated transfection of HBx into the Huh7 cell line. MTT, Annexin V/PI, and cell cycle assay were used for determining the cellular growth inhibition, apoptosis, and growth arrest, respectively, after treatment with chemical drug. We further used tumor-bearing mice model to compare the tumor growth inhibition efficacy of ADM and 5-FU between the Huh7-HBx group and the control group, as well as the ADM + IFN-alpha or ADM + IMD treated group and the ADM treated group. SQ-Real time-PCR was performed to analyze the expression of MDR-associated genes and anti-apoptotic genes. Moreover, immunofluorescence and Western blotting were used to determine the subcellular localization of p65 and the phosphorylation of IkappaBalpha. RESULTS: The IC50 values of Huh7-HBx cells against ADM and Amn were 2.317 and 1.828-folds higher than those of Huh7-3.1 cells, respectively. The apoptosis ratio and growth arrest was significantly lower in Huh7-HBx cells after treatment with ADM. The in vivo experiment also confirmed that the Huh7-HBx group was much more resistant to ADM or 5-FU than the control. Furthermore, the expression of MDR-associated genes, such as MDR1, MRP1, LRP1, and ABCG2, were significantly up-regulated in Huh7-HBx cells, and the NF-kappaB pathway was activated after HBx gene transfection in Huh7 cells. However, combined with IFN-alpha in ADM treatment, the HBx induced drug-resistance in Huh7-HBx cells can be partly abolished in in vitro and in vivo models. Moreover, we found that the NF-kappaB canonical pathway was affected by IFN-alpha treatment, and the expression of anti-apoptotic genes, such as Gadd45beta, Survivin, and c-IAP-1 was down-regulated by IFN-alpha treatment in a dose-dependent manner. CONCLUSIONS: HBx protein can induce MDR of HBV-

related HCC by activating the NF-kappaB pathway, which can be partly abolished by IFN-alpha treatment.

[1004]

**TÍTULO / TITLE:** - Natural Borneol, a Monoterpenoid Compound, Potentiates Selenocystine-Induced Apoptosis in Human Hepatocellular Carcinoma Cells by Enhancement of Cellular Uptake and Activation of ROS-Mediated DNA Damage.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 20;8(5):e63502. doi: 10.1371/journal.pone.0063502. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063502](#)

**AUTORES / AUTHORS:** - Su J; Lai H; Chen J; Li L; Wong YS; Chen T; Li X

**INSTITUCIÓN / INSTITUTION:** - College of Light Industry and Food Sciences, South China University of Technology, Guangzhou, China.

**RESUMEN / SUMMARY:** - Selenocystine (SeC) has been identified as a novel compound with broad-spectrum anticancer activities. Natural borneol (NB) is a monoterpenoid compound that has been used as a promoter of drug absorption. In the present study, we demonstrated that NB significantly enhanced the cellular uptake of SeC and potentiated its antiproliferative activity on HepG2 cells by induction of apoptosis. NB effectively synergized with SeC to reduce cancer cell growth through the triggering apoptotic cell death. Further mechanistic studies by Western blotting showed that treatment of the cells with NB and SeC activated the intrinsic apoptotic pathway by regulation of pro-survival and pro-apoptotic Bcl-2 family proteins. Treatment of the cells with NB and SeC induced the activation of p38MAPK and inactivation of Akt and ERK. NB also potentiated SeC to trigger intracellular ROS generation and DNA strand breaks as examined by Comet assay. Moreover, the thiol-reducing antioxidants effectively blocked the occurrence of cell apoptosis, which confirmed the important role of ROS in cell apoptosis. Taken together, these results reveal that NB strongly potentiates SeC-induced apoptosis in cancer cells by enhancement of cellular uptake and activation of ROS-mediated DNA damage. NB could be further developed as a chemosensitizer of SeC in treatment of human cancers.

[1005]

**TÍTULO / TITLE:** - Biomarkers and molecular testing for early detection, diagnosis, and therapeutic prediction of lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Thorac Surg Clin. 2013 May;23(2):211-24. doi: 10.1016/j.thorsurg.2013.01.002. Epub 2013 Feb 15.

●●Enlace al texto completo (gratis o de pago)

[1016/j.thorsurg.2013.01.002](#)

**AUTORES / AUTHORS:** - Pass HI; Beer DG; Joseph S; Massion P

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**RESUMEN / SUMMARY:** - The search for biomarkers in the management of lung cancer involves the use of multiple platforms to examine changes in gene, protein, and microRNA expression. Multiple studies have been published in an attempt to describe early detection, diagnostic, prognostic, and predictive biomarkers using chiefly tissues and blood elements. Studies are characterized by a lack of commonality of specific biomarkers, and a lack of validated, clinically useful markers. The future of biomarker discovery as a means of tailoring therapy for patients with lung cancer will involve next-generation sequencing along with collaborative efforts to integrate and validate candidate markers.

[1006]

**TÍTULO / TITLE:** - Decreased expression of RNA-binding motif protein 3 correlates with tumour progression and poor prognosis in urothelial bladder cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Urol. 2013 Apr 8;13:17. doi: 10.1186/1471-2490-13-17.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2490-13-17](#)

**AUTORES / AUTHORS:** - Boman K; Segersten U; Ahlgren G; Eberhard J; Uhlen M; Jirstrom K; Malmstrom PU

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**RESUMEN / SUMMARY:** - BACKGROUND: Low nuclear expression of the RNA-binding motif protein 3 (RBM3) has previously been found to be associated with poor prognosis in several cancer forms e.g. breast, ovarian, colorectal, prostate cancer and malignant melanoma. The aim of this study was to examine the prognostic impact of RBM3 expression in urinary bladder cancer. METHODS: Immunohistochemical RBM3 expression was examined in tumours from 343 patients with urothelial bladder cancer. Chi-square and Spearman's correlation tests were applied to explore associations between RBM3 expression and clinicopathological characteristics. The impact of RBM3 expression on disease-specific survival (DSS), 5-year overall survival (OS) and progression-free survival (PFS) was assessed by Kaplan-Meier analysis and Cox proportional hazards modelling. RESULTS: Reduced nuclear RBM3 expression was significantly associated with more advanced tumour (T) stage ( $p < 0.001$ ) and high grade tumours ( $p = 0.004$ ). Negative RBM3 expression was associated with a significantly shorter DSS (HR=2.55; 95% CI 1.68-3.86) and 5-year OS (HR=2.10; 95% CI 1.56-2.82), also in multivariable analysis (HR=1.65; 95% CI

1.07-2.53 for DSS and HR=1.54; 95% CI 1.13-2.10 for 5-year OS). In patients with Ta and T1 tumours expressing reduced RBM3 levels, Kaplan-Meier analysis revealed a significantly shorter PFS (p=0.048) and 5-year OS (p=0.006). CONCLUSION: Loss of RBM3 expression is associated with clinically more aggressive tumours and an independent factor of poor prognosis in patients with urothelial bladder cancer and a potentially useful biomarker for treatment stratification and surveillance of disease progression.

[1007]

**TÍTULO / TITLE:** - Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic value.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS Med. 2013 May;10(5):e1001453. doi: 10.1371/journal.pmed.1001453. Epub 2013 May 21.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pmed.1001453](#)

**AUTORES / AUTHORS:** - Marisa L; de Reynies A; Duval A; Selves J; Gaub MP; Vescovo L; Etienne-Grimaldi MC; Schiappa R; Guenot D; Ayadi M; Kirzin S; Chazal M; Flejou JF; Benchimol D; Berger A; Lagarde A; Pencreach E; Piard F; Elias D; Parc Y; Olschwang S; Milano G; Laurent-Puig P; Boige V

**INSTITUCIÓN / INSTITUTION:** - “Cartes d’Identite des Tumeurs” Program, Ligue Nationale Contre le Cancer, Paris, France.

**RESUMEN / SUMMARY:** - BACKGROUND: Colon cancer (CC) pathological staging fails to accurately predict recurrence, and to date, no gene expression signature has proven reliable for prognosis stratification in clinical practice, perhaps because CC is a heterogeneous disease. The aim of this study was to establish a comprehensive molecular classification of CC based on mRNA expression profile analyses. METHODS AND FINDINGS: Fresh-frozen primary tumor samples from a large multicenter cohort of 750 patients with stage I to IV CC who underwent surgery between 1987 and 2007 in seven centers were characterized for common DNA alterations, including BRAF, KRAS, and TP53 mutations, CpG island methylator phenotype, mismatch repair status, and chromosomal instability status, and were screened with whole genome and transcriptome arrays. 566 samples fulfilled RNA quality requirements. Unsupervised consensus hierarchical clustering applied to gene expression data from a discovery subset of 443 CC samples identified six molecular subtypes. These subtypes were associated with distinct clinicopathological characteristics, molecular alterations, specific enrichments of supervised gene expression signatures (stem cell phenotype-like, normal-like, serrated CC phenotype-like), and deregulated signaling pathways. Based on their main biological characteristics, we distinguished a deficient mismatch repair subtype, a KRAS mutant subtype, a cancer stem cell subtype, and three chromosomal instability subtypes, including one associated with down-regulated immune pathways, one with up-regulation of the Wnt pathway, and one displaying a

normal-like gene expression profile. The classification was validated in the remaining 123 samples plus an independent set of 1,058 CC samples, including eight public datasets. Furthermore, prognosis was analyzed in the subset of stage II-III CC samples. The subtypes C4 and C6, but not the subtypes C1, C2, C3, and C5, were independently associated with shorter relapse-free survival, even after adjusting for age, sex, stage, and the emerging prognostic classifier Oncotype DX Colon Cancer Assay recurrence score (hazard ratio 1.5, 95% CI 1.1-2.1,  $p = 0.0097$ ). However, a limitation of this study is that information on tumor grade and number of nodes examined was not available.

**CONCLUSIONS:** We describe the first, to our knowledge, robust transcriptome-based classification of CC that improves the current disease stratification based on clinicopathological variables and common DNA markers. The biological relevance of these subtypes is illustrated by significant differences in prognosis. This analysis provides possibilities for improving prognostic models and therapeutic strategies. In conclusion, we report a new classification of CC into six molecular subtypes that arise through distinct biological pathways. Please see later in the article for the Editors' Summary.

[1008]

**TÍTULO / TITLE:** - IP3R2 levels dictate the apoptotic sensitivity of diffuse large B-cell lymphoma cells to an IP3R-derived peptide targeting the BH4 domain of Bcl-2.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 May 16;4:e632. doi: 10.1038/cddis.2013.140.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.140](#)

**AUTORES / AUTHORS:** - Akl H; Monaco G; La Rovere R; Welkenhuyzen K; Kiviluoto S; Vervliet T; Molgo J; Distelhorst CW; Missiaen L; Mikoshiba K; Parys JB; De Smedt H; Bultynck G

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Molecular and Cellular Signaling, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.

**RESUMEN / SUMMARY:** - Disrupting inositol 1,4,5-trisphosphate (IP3) receptor (IP3R)/B-cell lymphoma 2 (Bcl-2) complexes using a cell-permeable peptide (stabilized TAT-fused IP3R-derived peptide (TAT-IDP(S))) that selectively targets the BH4 domain of Bcl-2 but not that of B-cell lymphoma 2-extra large (Bcl-XL) potentiated pro-apoptotic Ca(2+) signaling in chronic lymphocytic leukemia cells. However, the molecular mechanisms rendering cancer cells but not normal cells particularly sensitive to disrupting IP3R/Bcl-2 complexes are poorly understood. Therefore, we studied the effect of TAT-IDP(S) in a more heterogeneous Bcl-2-dependent cancer model using a set of 'primed to death' diffuse large B-cell lymphoma (DL-BCL) cell lines containing elevated Bcl-2 levels. We discovered a large heterogeneity in the apoptotic responses of these cells to TAT-IDP(S) with SU-DHL-4 being most sensitive and OCI-LY-1 being most resistant. This sensitivity strongly correlated with the ability of TAT-

IDP(S) to promote IP3R-mediated Ca(2+) release. Although total IP3R-expression levels were very similar among SU-DHL-4 and OCI-LY-1, we discovered that the IP3R2-protein level was the highest for SU-DHL-4 and the lowest for OCI-LY-1. Strikingly, TAT-IDP(S)-induced Ca(2+) rise and apoptosis in the different DL-BCL cell lines strongly correlated with their IP3R2-protein level, but not with IP3R1-, IP3R3- or total IP3R-expression levels. Inhibiting or knocking down IP3R2 activity in SU-DHL-4-reduced TAT-IDP(S)-induced apoptosis, which is compatible with its ability to dissociate Bcl-2 from IP3R2 and to promote IP3-induced pro-apoptotic Ca(2+) signaling. Thus, certain chronically activated B-cell lymphoma cells are addicted to high Bcl-2 levels for their survival not only to neutralize pro-apoptotic Bcl-2-family members but also to suppress IP3R hyperactivity. In particular, cancer cells expressing high levels of IP3R2 are addicted to IP3R/Bcl-2 complex formation and disruption of these complexes using peptide tools results in pro-apoptotic Ca(2+) signaling and cell death.

[1009]

**TÍTULO / TITLE:** - Missense allele of a single nucleotide polymorphism rs2294008 attenuated antitumor effects of prostate stem cell antigen in gallbladder cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Carcinog. 2013 Mar 16;12:4. doi: 10.4103/1477-3163.109030. Print 2013.

●●Enlace al texto completo (gratis o de pago) [4103/1477-3163.109030](#)

**AUTORES / AUTHORS:** - Ono H; Chihara D; Chiwaki F; Yanagihara K; Sasaki H; Sakamoto H; Tanaka H; Yoshida T; Saeki N; Matsuo K

**INSTITUCIÓN / INSTITUTION:** - Division of Genetics, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: Prostate stem cell antigen (PSCA), an organ-dependent tumor suppressor, is down regulated in gallbladder cancer (GBC). It is anticipated that the missense allele C of the single nucleotide polymorphism (SNP) rs2294008 (T/C) in the translation initiation codon of the gene affects the gene's biological function and has some influence on GBC susceptibility. We examined the biological effect of the C allele on the function of the gene and the relation between the C allele and GBC susceptibility.

**MATERIALS AND METHODS:** Functional analysis of the SNP was conducted by introducing PSCA cDNA harboring the allele to a GBC cell line TGBC-1TKB and performing colony formation assays in vitro and tumor formation assays in mice. The effect on transcriptional regulation was assessed by reporter assays. The association study was conducted on 44 Japanese GBC cases and 173 controls. **RESULTS:** The PSCA cDNA harboring the C allele showed lower cell growth inhibition activity (20% reduction) than that with the T allele.

Concordantly, when injected into subcutaneous tissues of mice, the GBC cell line stably expressing the cDNA with the C allele formed tumors of almost the

same size as that of the control cells, but the cell line expressing the cDNA with the T allele showed slower growth. The upstream DNA fragment harboring the C allele had more transcriptional activity than that with the T allele. The C allele showed positive correlation to GBC but no statistical significant odds ratio (OR = 1.77, 95% confidence interval 0.85-3.70, P value = 0.127 in dominant model). CONCLUSIONS: The missense allele was shown to have a biological effect, attenuating antitumor activities of PSCA, and consequently it may be a potential risk for GBC development. An association study in a larger sample size may reveal a significant association between the allele and GBC.

[1010]

**TÍTULO / TITLE:** - Identification of nine genomic regions of amplification in urothelial carcinoma, correlation with stage, and potential prognostic and therapeutic value.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 4;8(4):e60927. doi: 10.1371/journal.pone.0060927. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060927](http://dx.doi.org/10.1371/journal.pone.0060927)

**AUTORES / AUTHORS:** - Chekaluk Y; Wu CL; Rosenberg J; Riester M; Dai Q; Lin S; Guo Y; McDougal WS; Kwiatkowski DJ

**INSTITUCIÓN / INSTITUTION:** - Division of Translational Medicine, Brigham and Women's Hospital, Boston, Massachusetts, United States of America.

**RESUMEN / SUMMARY:** - We performed a genome wide analysis of 164 urothelial carcinoma samples and 27 bladder cancer cell lines to identify copy number changes associated with disease characteristics, and examined the association of amplification events with stage and grade of disease. Multiplex inversion probe (MIP) analysis, a recently developed genomic technique, was used to study 80 urothelial carcinomas to identify mutations and copy number changes. Selected amplification events were then analyzed in a validation cohort of 84 bladder cancers by multiplex ligation-dependent probe assay (MLPA). In the MIP analysis, 44 regions of significant copy number change were identified using GISTIC. Nine gene-containing regions of amplification were selected for validation in the second cohort by MLPA. Amplification events at these 9 genomic regions were found to correlate strongly with stage, being seen in only 2 of 23 (9%) Ta grade 1 or 1-2 cancers, in contrast to 31 of 61 (51%) Ta grade 3 and T2 grade 2 cancers,  $p < 0.001$ . These observations suggest that analysis of genomic amplification of these 9 regions might help distinguish non-invasive from invasive urothelial carcinoma, although further study is required. Both MIP and MLPA methods perform well on formalin-fixed paraffin-embedded DNA, enhancing their potential clinical use. Furthermore several of the amplified genes identified here (ERBB2, MDM2, CCND1) are potential therapeutic targets.

[1011]

**TÍTULO / TITLE:** - Combination effect of paclitaxel and hyaluronic acid on cancer stem-like side population cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biomed Nanotechnol. 2013 Feb;9(2):299-302.

**AUTORES / AUTHORS:** - Lee H; Kim JB; Park SY; Kim SS; Kim H

**INSTITUCIÓN / INSTITUTION:** - Department of Chemical and Biomolecular Engineering, Sogang University, #1 Shinsu-dong, Mapo-gu, Seoul 121-742, Republic of Korea.

**RESUMEN / SUMMARY:** - Cancer recurrence is the main cause of chemotherapeutic treatment failure. The mechanisms driving cancer recurrence may be due to very rare subpopulation cells, cancer stem-like cells (CSCs). Therefore, the early detection and better treatment of cancer stem-like cells are of great interest. In this study, we investigated how to eliminate the side population cells (SP), which have the characteristics of cancer stem-like cells, and also show chemotherapy resistance. Fluorescence-activated cell sorting (FACS) were used to sort SP and non-SP cells from human liver cancers, Huh-7 Hyaluronic acid (HA), which is an abundant component in the extracellular matrix, is known to involve in proliferation of normal and cancer cells. Herein, we investigated the effect of HA component on chemotherapy against SP cells. Cell growth inhibitory effects of the paclitaxel (PTX) chemotherapy combined with the HA component on SP cells of Huh-7 was determined using the trypan blue dye exclusion test. PTX combined with HA was found to show more increased inhibition of cell growth in both SP and non-SP cells, compared to free PTX treatment. In conclusion, SP cells of Huh-7 shows chemotherapeutic drug resistance due to the over-expressed efflux pumps. HA proposed one of possibilities to overcome the limitation of chemotherapy against cancer stem-like cells.

[1012]

**TÍTULO / TITLE:** - Proliferation enhanced by NGF-NTRK1 signaling makes pancreatic cancer cells more sensitive to 2DG-induced apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Med Sci. 2013;10(5):634-40. doi: 10.7150/ijms.5547. Epub 2013 Mar 23.

●●Enlace al texto completo (gratis o de pago) [7150/ijms.5547](#)

**AUTORES / AUTHORS:** - Cheng Y; Diao DM; Zhang H; Song YC; Dang CX

**INSTITUCIÓN / INSTITUTION:** - The Department of Surgical Oncology the First Affiliated Hospital, Xi'an Jiaotong University College of Medicine, 277 W. Yanta Road, Xi'an, Shaanxi 710061, China.

**RESUMEN / SUMMARY:** - Rapidly proliferating cancer cells rely on increased glucose consumption for survival. The glucose analog 2-deoxy-D-glucose (2DG) cannot complete glycolysis and inhibits the growth of many types of cancers. It is unknown whether reduced glycolysis inhibits the growth of

pancreatic cancer. Activation of nerve growth factor (NGF)-neurotrophic tyrosine kinase receptor type 1 (NTRK1) signaling leads to enhanced proliferation of these cells. We investigated the effect of 2DG treatment on the viability of NTRK1-transfected pancreatic cancer cells. After treatment with 2DG, the viability of pancreatic cancer cells was evaluated by MTT assay. SB203580 (a specific inhibitor of the p38-MAPK pathway) and PD98059 (an MAP2K1 [mitogen-activated protein kinase kinase 1, previously, MEK1] inhibitor) were used to inhibit p38-MAPK and ERKs, respectively. The percentage of apoptotic cells was determined by flow cytometry. Overexpression of NTRK1 in pancreatic cancer cells resulted in increased cell proliferation, which was reduced by PD98059-mediated inhibition of ERKs but not by suppression of p38-MAPK with SB203580. After treatment with 2DG, the percentage of apoptotic cells was greater in those with high expression of NTRK1 than in cells with low NTRK1 expression. Blocking the p38-MAPK pathway with SB203580 effectively abolished the apoptosis induced by 2DG. We conclude that pancreatic cancer cells with a high expression of NTRK1 are more sensitive to 2DG-induced apoptosis, through the p38-MAPK pathway.

[1013]

**TÍTULO / TITLE:** - Apoptotic effect of cisplatin and cordycepin on OC3 human oral cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin J Integr Med. 2013 Apr 1.

●●Enlace al texto completo (gratis o de pago) [1007/s11655-013-1453-](#)

[3](#)

**AUTORES / AUTHORS:** - Chen YH; Hao LJ; Hung CP; Chen JW; Leu SF; Huang BM

**INSTITUCIÓN / INSTITUTION:** - Department of Anesthesia, Chi-Mei Medical Center, Liouying, Tainan, Taiwan, China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To evaluate apoptotic effects of cisplatin and cordycepin as single agent or in combination with cytotoxicity in oral cancer cells. **METHODS:** The influences of cisplatin (2.5 µg/mL) and/or cordycepin treatment (10 or 100 µmol/L) to human OC3 oral cancer cell line were investigated by morphological observation for cell death appearance, methylthiazolotetrazolium (MTT) assay for cell viability, flow cytometry assay for cell apoptosis, and Western blotting for apoptotic protein expressions. **RESULTS:** Data demonstrated that co-administration of cisplatin (2.5 µg/mL) and cordycepin (10 or 100 µmol/L) resulted in the enhancement of OC3 cell apoptosis compared to cisplatin or cordycepin alone treatment (24 h), respectively ( $P < 0.05$ ). In flow cytometry assay, percentage of cells arrested at subG1 phase with co-treatment of cordycepin and cisplatin (30%) was significantly higher than cisplatin (5%) or cordycepin (12%) alone group ( $P < 0.05$ ), confirming a synergistically apoptotic effect of cordycepin and cisplatin. In cellular mechanism study, co-treatment of cordycepin and cisplatin

induced more stress-activated protein kinase/Jun terminal kinase (JNK), the expressions of caspase-7, and the cleavage of poly ADP-ribose polymerase (PARP) as compared to cisplatin or cordycepin alone treatment ( $P < 0.05$ ).  
CONCLUSION: Cisplatin and cordycepin possess synergistically apoptotic effect through the activation of JNK/caspase-7/PARP pathway in human OC3 oral cancer cell line.

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[1014]

**TÍTULO / TITLE:** - Prognostic assessment of apoptotic gene polymorphisms in non-small cell lung cancer in Chinese.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biomed Res. 2013 May;27(3):231-8. doi: 10.7555/JBR.27.20130014. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [7555/JBR.27.20130014](#)

**AUTORES / AUTHORS:** - Cao S; Wang C; Huang X; Dai J; Hu L; Liu Y; Chen J; Ma H; Jin G; Hu Z; Xu L; Shen H

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology and Biostatistics, Modern Toxicology Laboratory of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 210009, China;

**RESUMEN / SUMMARY:** - Apoptosis plays a key role in inhibiting tumor growth, progression and resistance to anti-tumor therapy. We hypothesized that genetic variants in apoptotic genes may affect the prognosis of lung cancer. To test this hypothesis, we selected 38 potentially functional single nucleotide polymorphisms (SNPs) from 12 genes (BAX, BCL2, BID, CASP3, CASP6, CASP7, CASP8, CASP9, CASP10, FAS, FASLG and MCL1) involved in apoptosis to assess their prognostic significance in lung cancer in a Chinese case cohort with 568 non-small cell lung cancer (NSCLC) patients. Thirty-five SNPs passing quality control underwent association analyses, 11 of which were shown to be significantly associated with NSCLC survival ( $P < 0.05$ ). After Cox stepwise regression analyses, 3 SNPs were independently associated with the outcome of NSCLC (BID rs8190315:  $P = 0.003$ ; CASP9 rs4645981:  $P = 0.007$  and FAS rs1800682:  $P = 0.016$ ). A favorable survival of NSCLC was significantly associated with the genotypes of BID rs8190315 AG/GG (adjusted HR = 0.65, 95% CI: 0.49-0.88), CASP9 rs4645981 AA (HR = 0.22, 95% CI: 0.07-0.69) and FAS rs1800682 GG (adjusted HR = 0.67, 95% CI: 0.46-0.97). Time-dependent receiver operation curve (ROC) analysis revealed that the area under curve (AUC) at year 5 was significantly increased from 0.762 to 0.819 after adding the risk score of these 3 SNPs to the clinical risk score. The remaining 32 SNPs were not significantly associated with NSCLC prognosis after adjustment for these 3 SNPs. These findings indicate that BID rs8190315, CASP9 rs4645981 and FAS rs1800682 polymorphisms in the apoptotic pathway may be involved in the prognosis of NSCLC in the Chinese population.

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[1015]

**TÍTULO / TITLE:** - Autophagy enhances the aggressiveness of human colorectal cancer cells and their ability to adapt to apoptotic stimulus.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Med. 2012 Jun;9(2):105-10. doi: 10.3969/j.issn.2095-3941.2012.02.004.

●●Enlace al texto completo (gratis o de pago) [3969/j.issn.2095-3941.2012.02.004](#)

**AUTORES / AUTHORS:** - Zheng HY; Zhang XY; Wang XF; Sun BC

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, The Second Hospital of Tianjin Medical University, Tianjin 300211, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: To investigate LC3B-II and active caspase-3 expression in human colorectal cancer to elucidate the role of autophagy, and to explore the relationship of autophagy with apoptosis in human colorectal cancer. METHODS: LC3B expression was detected by immunohistochemistry in 53 human colorectal cancer tissues and 20 normal colon tissues. The protein levels of LC3B-II and active caspase-3 were also determined by Western blot analysis in 23 human colorectal cancer tissues and 10 normal colon tissues. RESULTS: LC3B was expressed both in cancer cells and normal epithelial cells. LC3B expression in the peripheral area of cancer tissues was correlated with several clinicopathological factors, including tumor differentiation (P=0.002), growth pattern of the tumor margin (P=0.028), pN (P=0.002), pStage (P=0.032), as well as vessel and nerve plexus invasion (P=0.002). The protein level of LC3B-II in cancer tissue was significantly higher than in normal tissue (P=0.038), but the expression of active forms of procaspase-3 in cancer tissue was lower (P=0.041). There was a statistically significant positive correlation between the expression levels of LC3B-II and the active forms of procaspase-3 (r=0.537, P=0.008). CONCLUSIONS: Autophagy has a prosurvival role in human colorectal cancer. Autophagy enhances the aggressiveness of colorectal cancer cells and their ability to adapt to apoptotic stimulus.

[1016]

**TÍTULO / TITLE:** - MicroRNA-495 inhibits proliferation of glioblastoma multiforme cells by downregulating cyclin-dependent kinase 6.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg Oncol. 2013 Apr 17;11:87. doi: 10.1186/1477-7819-11-87.

●●Enlace al texto completo (gratis o de pago) [1186/1477-7819-11-87](#)

**AUTORES / AUTHORS:** - Chen SM; Chen HC; Chen SJ; Huang CY; Chen PY; Wu TW; Feng LY; Tsai HC; Lui TN; Hsueh C; Wei KC

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Chang Gung Memorial Hospital at Linkou, Chang Gung University, No,5 Fu-Shin Street, Kweishan, Taoyuan 333, Taiwan. [anray5319@cgmh.org.tw](mailto:anray5319@cgmh.org.tw).

**RESUMEN / SUMMARY:** - BACKGROUND: Glioblastoma multiforme (GBM) is the most aggressive type of glioma and carries the poorest chances of survival. There is therefore an urgent need to understand the mechanisms of glioma tumorigenesis and develop or improve therapeutics. The aim of this study was to assess the possible prognostic value of cyclin-dependent kinase 6 (CDK6) and the effects of microRNA-495 (miR-495) manipulation on CDK6 expression and cell survival in glioma cells. METHODS: Analyses of clinical specimens from GBM patients were used. Expression of CDK6 was analyzed by real-time polymerase chain reaction (RT-PCR), Western blotting, and immunohistochemistry. Expression of CDK6 was also analyzed after over-expression of miR-495 in T98 cells; both cell proliferation and RB phosphorylation were examined. Cell proliferation, cell cycle distribution, and RB phosphorylation were also examined after knockdown of CDK6 in U87-MG and T98 cells. RESULTS: Analyses of clinical specimens from GBM patients identified that CDK6 is significantly expressed in gliomas. CDK6 antigen expression was higher in tumor cores and margins than in adjacent normal brain tissues, and higher levels of CDK6 expression in the tumor margin correlated with decreased survival. Over-expression of miR-495 in T98 cells downregulated the expression of CDK6 and inhibited retinoblastoma phosphorylation, and knockdown of CDK6 in U87-MG and T98 cells by siRNAs resulted in cell cycle arrest at the G1/S transition and inhibition of cell proliferation. CONCLUSIONS: This study revealed miR-495 is down-regulated in glioma tissues. Furthermore, miR-495 regulated CDK6 expression and involved in glioma cell growth inhibition, which indicated the possible role of miR-495 in tumor progression.

[1017]

**TÍTULO / TITLE:** - Rapamycin Inhibits IGF-1-Mediated Up-Regulation of MDM2 and Sensitizes Cancer Cells to Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 30;8(4):e63179. doi: 10.1371/journal.pone.0063179. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063179](http://1371/journal.pone.0063179)

**AUTORES / AUTHORS:** - Du W; Yi Y; Zhang H; Bergholz J; Wu J; Ying H; Zhang Y; Xiao ZX

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Boston University School of Medicine, Boston, Massachusetts, United States of America.

**RESUMEN / SUMMARY:** - The Murine Double Minute 2 (MDM2) protein is a key regulator of cell proliferation and apoptosis that acts primarily by inhibiting the p53 tumor suppressor. Similarly, the PI3-Kinase (PI3K)/AKT pathway is critical for growth factor-mediated cell survival. Additionally, it has been reported that AKT can directly phosphorylate and activate MDM2. In this study, we show that IGF-1 up-regulates MDM2 protein levels in a PI3K/AKT-dependent manner.

Inhibition of mTOR by rapamycin or expression of a dominant negative eukaryotic initiation factor 4E binding protein 1 (4EBP1) mutant protein, as well as ablation of eukaryotic initiation factor 4E (eIF4E), efficiently abolishes IGF-1-mediated up-regulation of MDM2. In addition, we show that rapamycin effectively inhibits MDM2 expression and sensitizes cancer cells to chemotherapy. Taken together, this study reveals a novel mechanism by which IGF-1 activates MDM2 via the mTOR pathway, and that pharmacologic inhibition of mTOR combined with chemotherapy may be more effective in treatment of a subset of cancers harboring increased MDM2 activation.

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[1018]

**TÍTULO / TITLE:** - Analysis of the mRNA expression of chemotherapy-related genes in colorectal carcinoma using the danenberg tumor profile method.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Oncol. 2013;2013:386906. doi: 10.1155/2013/386906. Epub 2013 Mar 16.

●●Enlace al texto completo (gratis o de pago) [1155/2013/386906](#)

**AUTORES / AUTHORS:** - Sasaki S; Watanabe T; Nakayama H

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Omori Red Cross Hospital, 4-30-1, Chuo, Ota-ku, Tokyo 143-8527, Japan.

**RESUMEN / SUMMARY:** - The establishment of individualized chemotherapy for colorectal carcinoma based on the expression of genes involved in chemotherapeutic sensitivity or prognosis is necessary. To achieve this, the expression profiles of genes within tumors and their relationship to clinicopathological factors must be elucidated. Here, we selected 10 genes (TS, DPD, TP, FPGS, GGH, DHFR, ERCC1, TOPO-1, VEGF, and EGFR), examined differences in their mRNA expression between the upper and lower thirds of tumors by laser-captured microdissection and real-time RT-PCR (the Danenberg tumor profile), and analyzed the relationships between their expression profiles and clinicopathological factors. Interestingly, the mRNA expression of DPD, TP, and VEGF was significantly higher in the lower third than in the upper third of tumors ( $P = 0.044$ ,  $0.023$ , and  $0.013$ , resp.). Furthermore, increased ERCC1 mRNA expression in the lower third of tumors correlated with recurrence ( $P = 0.049$ ), and VEGF mRNA expression was significantly higher in cases with recurrence than in cases without recurrence, both in the upper and lower thirds of tumors ( $P = 0.018$  and  $0.036$ , resp.). These results implied that heterogeneity in DPD, TP, and VEGF expression may exist in colorectal carcinoma and that ERCC-1 and VEGF may be markers predicting recurrence after curative operation.

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[1019]

**TÍTULO / TITLE:** - Impact of the p53 status of tumor cells on extrinsic and intrinsic apoptosis signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Commun Signal. 2013 Apr 17;11(1):27. doi: 10.1186/1478-811X-11-27.

●●Enlace al texto completo (gratis o de pago) [1186/1478-811X-11-27](https://doi.org/10.1186/1478-811X-11-27)

**AUTORES / AUTHORS:** - Wachter F; Grunert M; Blaj C; Weinstock DM; Jeremias I; Ehrhardt H

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**RESUMEN / SUMMARY:** - BACKGROUND: The p53 protein is the best studied target in human cancer. For decades, p53 has been believed to act mainly as a tumor suppressor and by transcriptional regulation. Only recently, the complex and diverse function of p53 has attracted more attention. Using several molecular approaches, we studied the impact of different p53 variants on extrinsic and intrinsic apoptosis signaling. RESULTS: We reproduced the previously published results within intrinsic apoptosis induction: while wild-type p53 promoted cell death, different p53 mutations reduced apoptosis sensitivity. The prediction of the impact of the p53 status on the extrinsic cell death induction was much more complex. The presence of p53 in tumor cell lines and primary xenograft tumor cells resulted in either augmented, unchanged or reduced cell death. The substitution of wild-type p53 by mutant p53 did not affect the extrinsic apoptosis inducing capacity. CONCLUSIONS: In summary, we have identified a non-expected impact of p53 on extrinsic cell death induction. We suggest that the impact of the p53 status of tumor cells on extrinsic apoptosis signaling should be studied in detail especially in the context of therapeutic approaches that aim to restore p53 function to facilitate cell death via the extrinsic apoptosis pathway.

[1020]

**TÍTULO / TITLE:** - Deciphering the signaling networks underlying simvastatin-induced apoptosis in human cancer cells: evidence for non-canonical activation of RhoA and Rac1 GTPases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Apr 4;4:e568. doi: 10.1038/cddis.2013.103.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.103](https://doi.org/10.1038/cddis.2013.103)

**AUTORES / AUTHORS:** - Zhu Y; Casey PJ; Kumar AP; Pervaiz S

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

**RESUMEN / SUMMARY:** - Although statins are known to inhibit proliferation and induce death in a number of cancer cell types, the mechanisms through which downregulation of the mevalonate (MVA) pathway activates death signaling remain poorly understood. Here we set out to unravel the signaling networks downstream of the MVA pathway that mediate the death-inducing activity of simvastatin. Consistent with previous reports, exogenously added

geranylgeranylpyrophosphate, but not farnesylpyrophosphate, prevented simvastatin's growth-inhibitory effect, thereby suggesting the involvement of geranylgeranylated proteins such as Rho GTPases in the anticancer activity of simvastatin. Indeed, simvastatin treatment led to increased levels of unprenylated Ras homolog gene family, member A (RhoA), Ras-related C3 botulinum toxin substrate 1 (Rac1) and cell division cycle 42 (Cdc42). Intriguingly, instead of inhibiting the functions of Rho GTPases as was expected with loss of prenylation, simvastatin caused a paradoxical increase in the GTP-bound forms of RhoA, Rac1 and Cdc42. Furthermore, simvastatin disrupted the binding of Rho GTPases with the cytosolic inhibitor Rho GDIalpha, which provides a potential mechanism for GTP loading of the cytosolic Rho GTPases. We also show that the unprenylated RhoA- and Rac1-GTP retained at least part of their functional activities, as evidenced by the increase in intracellular superoxide production and JNK activation in response to simvastatin. Notably, blocking superoxide production attenuated JNK activation as well as cell death induced by simvastatin. Finally, we provide evidence for the involvement of the B-cell lymphoma protein 2 family, Bcl-2-interacting mediator (Bim), in a JNK-dependent manner, in the apoptosis-inducing activity of simvastatin. Taken together, our data highlight the critical role of non-canonical regulation of Rho GTPases and involvement of downstream superoxide-mediated activation of JNK pathway in the anticancer activity of simvastatin, which would have potential clinical implications.

[1021]

**TÍTULO / TITLE:** - PMS1077 sensitizes TNF-alpha induced apoptosis in human prostate cancer cells by blocking NF-kappaB signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 9;8(4):e61132. doi: 10.1371/journal.pone.0061132. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061132](https://doi.org/10.1371/journal.pone.0061132)

**AUTORES / AUTHORS:** - Shi J; Chen J; Serradji N; Xu X; Zhou H; Ma Y; Sun Z; Jiang P; Du Y; Yang J; Dong C; Wang Q

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, Lanzhou University, Lanzhou, China.

**RESUMEN / SUMMARY:** - Our previous studies have demonstrated that PMS1077, a platelet-activating factor (PAF) antagonist, could induce apoptosis of Raji cells. However, the mechanism of action has not yet been determined. The nuclear transcription factor-kappa B (NF-kappaB) signaling pathway plays a critical role in tumor cell survival, proliferation, invasion, metastasis, and angiogenesis, so we determined the effects of PMS1077 and its structural analogs on tumor necrosis factor-alpha (TNF-alpha) induced activation of NF-kappaB signaling. In this study, we found that PMS1077 inhibited TNF-alpha induced expression of the NF-kappaB regulated reporter gene in a dose

dependent manner. Western blot assay indicated that PMS1077 suppressed the TNF-alpha induced inhibitor of kappaB-alpha (IkappaB-alpha) phosphorylation, IkappaB-alpha degradation, and p65 phosphorylation. PMS1077 consistently blocked TNF-alpha induced p65 nuclear translocation as demonstrated in the immunofluorescence assay used. Docking studies by molecular modeling predicted that PMS1077 might interact directly with the IkappaB kinase-beta (IKK-beta) subunit. These results suggested that PMS1077 might suppress the activation of NF-kappaB by targeting IKK-beta involved in the NF-kappaB signaling pathway. Finally, we showed that PMS1077 sensitized cells to TNF-alpha induced apoptosis by suppressing the expression of NF-kappaB regulated anti-apoptotic genes. Our results reveal a novel function of PMS1077 on the NF-kappaB signaling pathway and imply that PMS1077 can be considered as an anti-tumor lead compound.

[1022]

**TÍTULO / TITLE:** - CSF-1R as an inhibitor of apoptosis and promoter of proliferation, migration and invasion of canine mammary cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Vet Res. 2013 Apr 5;9:65. doi: 10.1186/1746-6148-9-65.

●●Enlace al texto completo (gratis o de pago) [1186/1746-6148-9-65](#)

**AUTORES / AUTHORS:** - Krol M; Majchrzak K; Mucha J; Homa A; Bulkowska M; Jakubowska A; Karwicka M; Pawlowski KM; Motyl T

**INSTITUCIÓN / INSTITUTION:** - Department of Physiological Sciences, Faculty of Veterinary Medicine, Warsaw University of Life Sciences - WULS, Nowoursynowska 159, Warsaw, 02-776, Poland. [magdalena.krol@sggw.pl](mailto:magdalena.krol@sggw.pl).

**RESUMEN / SUMMARY:** - BACKGROUND: Tumor-associated macrophages (TAMs) have high impact on the cancer development because they can facilitate matrix invasion, angiogenesis, and tumor cell motility. It gives cancer cells the capacity to invade normal tissues and metastasize. The signaling of colony-stimulating factor-1 receptor (CSF-1R) which is an important regulator of proliferation and differentiation of monocytes and macrophages regulates most of the tissue macrophages. However, CSF-1R is expressed also in breast epithelial tissue during some physiological stages i.g.: pregnancy and lactation. Its expression has been also detected in various cancers. Our previous study has showed the expression of CSF-1R in all examined canine mammary tumors. Moreover, it strongly correlated with grade of malignancy and ability to metastasis. This study was therefore designed to characterize the role of CSF-1R in canine mammary cancer cells proliferation, apoptosis, migration, and invasion. As far as we know, the study presented hereby is a pioneering experiment in this field of veterinary medicine. RESULTS: We showed that csf-1r silencing significantly increased apoptosis (Annexin V test), decreased proliferation (measured as Ki67 expression) and decreased migration ("wound healing" assay) of canine mammary cancer cells. Treatment of these cells with

CSF-1 caused opposite effect. Moreover, csf-1r knock-down changed growth characteristics of highly invasive cell lines on Matrigel matrix, and significantly decreased the ability of these cells to invade matrix. CSF-1 treatment increased invasion of cancer cells. CONCLUSION: The evidence of the expression and functional role of the CSF-1R in canine mammary cancer cells indicate that CSF-1R targeting may be a good therapeutic approach.

[1023]

**TÍTULO / TITLE:** - Prognostic Significance of EBV Latent Membrane Protein 1 Expression in Lymphomas: Evidence from 15 Studies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 17;8(4):e60313. doi: 10.1371/journal.pone.0060313. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060313](#)

**AUTORES / AUTHORS:** - Mao Y; Lu MP; Lin H; Zhang da W; Liu Y; Li QD; Lv ZG; Xu JR; Chen RJ; Zhu J

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology-Head and Neck Surgery, Jiangsu Province Official Hospital, Nanjing, China ; Huadong Medical Institute of Biotechnology, Nanjing, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Epstein-Barr virus (EBV) infection has been associated with lymphoma development. EBV latent membrane protein 1 (LMP1) is essential for EBV-mediated transformation and progression of different human cells, including lymphocytes. This meta-analysis investigated LMP1 expression with prognosis of patients with lymphoma. METHODS: The electronic databases of PubMed, Embase, and Chinese Biomedicine Databases were searched. There were 15 published studies available for a random effects model analysis. Quality assessment was performed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. A funnel plot was used to investigate publication bias, and sources of heterogeneity were identified by meta-regression analysis. The combined hazard ratios (HR) and their corresponding 95% confidence intervals of LMP1 expression were calculated by comparison to the overall survival. RESULTS: Overall, there was no statistical significance found between LMP1 expression and survival of lymphoma patients (HR 1.25 [95% CI, 0.92-1.68]). In subgroup analyses, LMP1 expression was associated with survival in patients with non-Hodgkin lymphoma (NHL) (HR = 1.84, 95% CI: 1.02-3.34), but not with survival of patients with Hodgkin disease (HD) (HR = 1.03, 95% CI: 0.74-1.44). In addition, significant heterogeneity was present and the meta-regression revealed that the outcome of analysis was mainly influenced by the cutoff value. CONCLUSIONS: This meta-analysis demonstrated that LMP1 expression appears to be an unfavorable prognostic factor for overall survival of NHL patients. The data suggested that EBV infection and LMP1 expression may be an important factor for NHL development or progression.

[1024]

**TÍTULO / TITLE:** - Expression and prognostic role of c-Myb as a novel cell cycle protein in esophageal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 May 9.

●●Enlace al texto completo (gratis o de pago) [1007/s12094-013-1009-1](#)

**AUTORES / AUTHORS:** - Lu H; Wang Y; Huang Y; Shi H; Xue Q; Yang S; He S; Wang H

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiothoracic Surgery, Nantong University Cancer Hospital, Nantong University, Nantong, 226001, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: The c-Myb transcription factor controls differentiation and proliferation in hematopoietic and other cell types, and has latent in regulation during the cell cycle. Recent studies suggested that deregulation of c-Myb expression plays a key role in oncogenesis. To investigate the potential roles of c-Myb in esophageal carcinoma, expression of c-Myb was examined in human esophageal carcinoma samples. METHODS: Immunohistochemistry and Western blot analysis were performed for c-Myb in 87 esophageal carcinoma samples. The data were correlated with clinicopathological features. The univariate and multivariate survival analyses were also performed to determine their prognostic significance. RESULTS: c-Myb was overexpressed in esophageal carcinoma as compared with the adjacent normal tissue. High expression of c-Myb was associated with histological grade and was positively correlated with proliferation marker Ki-67 ( $P = 0.001$ ). Univariate analysis showed that c-Myb expression was associated with poor prognosis ( $P < 0.001$ ). Multivariate analysis indicated that c-Myb was an independent prognostic marker for esophageal carcinoma ( $P < 0.001$ ). While in vitro, following release from serum starvation of TE-1 esophageal carcinoma cell, the expression of c-Myb was upregulated. CONCLUSIONS: Our results suggested that c-Myb overexpression is involved in the pathogenesis of esophageal carcinoma; it may be a favorable independent poor prognostic parameter for esophageal carcinoma.

[1025]

**TÍTULO / TITLE:** - Association between ezrin protein expression and the prognosis of colorectal adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jul;8(1):61-6. doi: 10.3892/mmr.2013.1490. Epub 2013 May 24.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1490](#)

**AUTORES / AUTHORS:** - Lin LJ; Chen LT

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Imaging, Eastern Liaoning University School of Medicine, Dandong 118002, P.R. China.

**RESUMEN / SUMMARY:** - Ezrin is involved in maintaining cell structure and cell motility. Expression levels of the ezrin gene correlate with numerous human malignancies. The aim of this study was to explore the role of ezrin in tumor progression and the prognostic evaluation of colorectal adenocarcinoma (CRA). The levels of ezrin protein in 186 CRA samples were evaluated using immunohistochemistry. Furthermore, the correlation between the expression of ezrin and the clinicopathological features of CRA was evaluated with the chi<sup>2</sup> and Fisher's exact tests, survival rates were calculated using the Kaplan-Meier method, and the correlation between prognostic factors and patient survival was calculated by Cox analysis. Ezrin protein expression demonstrated an immunohistochemical cytoplasmic staining pattern in CRA. The difference between the positive rate of ezrin expression in CRA (38.7%, 72/186) and the adjacent normal mucosal tissues was deemed to be statistically significant (91.9%, 171/186; P=0.000). The positive rate of ezrin expression in cases with a large tumor, serosal invasion, lymph node (LN) metastasis, high LN ratio (LNR) and at a late tumor stage was significantly lower than in cases without these factors (P=0.044, P=0.032, P=0.002, P=0.011 and P=0.000, respectively). The 5-year survival rate of CRA without ezrin expression was lower than CRA with expression (P=0.000). Furthermore, analysis by Kaplan-Meier demonstrated that CRA cases with poor differentiation, serosal invasion and at a late tumor stage combined with no ezrin expression had a lower survival rate than cases that had these factors plus ezrin expression (P=0.000, respectively). Additionally, the non-expression of ezrin emerged as a significant independent prognostic factor in CRA prognosis (HR, 0.562; 95% CI, 0.404-0.783; P=0.001), in addition to the LNR (HR, 0.589; 95% CI, 0.369-0.939; P=0.026) and tumor stage (HR, 0.655; 95% CI, 0.487-0.880; P=0.005). This study demonstrated that ezrin may be useful to identify at-risk patients who may benefit from a more aggressive adjuvant therapy following tumor resection. Ezrin may serve as a useful therapeutic biomarker.

[1026]

**TÍTULO / TITLE:** - MicroRNA-21 Regulates the Invasion and Metastasis in Cholangiocarcinoma and May Be a Potential Biomarker for Cancer Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):829-34.

**AUTORES / AUTHORS:** - Huang Q; Liu L; Liu CH; You H; Shao F; Xie F; Lin XS; Hu SY; Zhang CH

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Affiliated Provincial Hospital of Anhui Medical University, Hefei, Anhui, China E-mail : 1452504862 @qq.com.

**RESUMEN / SUMMARY:** - Background: MicroRNAs are noncoding RNA molecules that posttranscriptionally regulate gene expression. The aim of this study was to

determine the role of microRNA-21 in cholangiocarcinomas and its relationship to cholangiocarcinoma RBE cell capacity for invasion and metastasis. Methods: MicroRNA-21 expression was investigated in 41 cases of cholangiocarcinoma samples by in situ hybridization and real-time PCR. Influence on cholangiocarcinoma cell line invasion and metastasis was analyzed with microRNA-21 transfected cells. In addition, regulation of reversion-inducing-cysteine-rich protein with kazal motifs (RECK) by microRNA-21 was elucidated to identify mechanisms. Results: In situ hybridization and real-time quantitative PCR results for patients with lymph node metastasis or perineural invasion showed significantly high expression of microRNA-21 ( $P < 0.05$ ). There was a dramatic decrease in cholangiocarcinoma cell line invasion and metastasis ability after microRNA-21 knockdown ( $P < 0.05$ ). However, overexpression significantly increased invasion and metastasis ( $P < 0.05$ ). Real-time PCR and Western-blot analysis showed that microRNA-21 could potentially inhibit RECK expression in RBE cells. Survival analysis showed that patients with higher expression levels of microRNA-21 more often had a poor prognosis ( $P < 0.05$ ). Conclusions: MicroRNA-21 may play an important role in cholangiocarcinoma invasion and metastasis, suggesting that MicroRNA-21 should be further evaluated as a biomarker for predicting cholangiocarcinoma prognosis.

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[1027]

**TÍTULO / TITLE:** - Identification of Serum MicroRNA-21 as a Biomarker for Early Detection and Prognosis in Human Epithelial Ovarian Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):1057-60.

**AUTORES / AUTHORS:** - Xu YZ; Xi QH; Ge WL; Zhang XQ

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Affiliated Hospital of Nan Tong University, Nan Tong, Jiangsu, China E-mail : [manuxiqh@163.com](mailto:manuxiqh@163.com).

**RESUMEN / SUMMARY:** - Recent investigations have confirmed up-regulation of serum miR-21 and its diagnostic and prognostic value in several human malignancies. In this study, we examined serum miR-21 levels in epithelial ovarian cancer (EOC) patients, and explored its association with clinicopathological factors and prognosis. The results showed significantly higher serum miR-21 levels in EOC patients than in healthy controls. In addition, increased serum miR-21 expression was correlated with advanced FIGO stage, high tumor grade, and shortened overall survival. These findings indicate that serum miR-21 may serve as a novel diagnostic and prognostic marker, and be used as a therapeutic target for the treatment of EOC.

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[1028]

**TÍTULO / TITLE:** - MicroRNAs as tumour suppressors in canine and human melanoma cells and as a prognostic factor in canine melanomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Vet Comp Oncol. 2013 Jun;11(2):113-23. doi: 10.1002/vco.306.

●●Enlace al texto completo (gratis o de pago) [1002/vco.306](#)

**AUTORES / AUTHORS:** - Noguchi S; Mori T; Hoshino Y; Yamada N; Maruo K; Akao Y

**INSTITUCIÓN / INSTITUTION:** - The United Graduate School of Veterinary Sciences, Gifu University, Gifu, Japan; The United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, Gifu, Japan.

**RESUMEN / SUMMARY:** - Malignant melanoma (MM) is one of the most aggressive cancers in dogs and in humans. However, the molecular mechanisms of its development and progression remain unclear. Presently, we examined the expression profile of microRNAs (miRs) in canine oral MM tissues and paired normal oral mucosa tissues by using the microRNA-microarray assay and quantitative RT-PCR. Importantly, a decreased expression of miR-203 was significantly associated with a shorter survival time. Also, miR-203 and -205 were markedly down-regulated in canine and human MM cell lines tested. Furthermore, the ectopic expression of miR-205 had a significant inhibitory effect on the cell growth of canine and human melanoma cells tested by targeting erbb3. Our data suggest that miR-203 is a new prognostic factor in canine oral MMs and that miR-205 functions as a tumour suppressor by targeting erbb3 in both canine and human MM cells.

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[1029]

**TÍTULO / TITLE:** - Long-Term Treatment with Erlotinib for EGFR Wild-Type Non-Small Cell Lung Cancer: A Case Report.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Case Rep Oncol. 2013 Mar 29;6(1):189-96. doi: 10.1159/000350680. Print 2013 Jan.

●●Enlace al texto completo (gratis o de pago) [1159/000350680](#)

**AUTORES / AUTHORS:** - Polychronidou G; Papakotoulas P

**INSTITUCIÓN / INSTITUTION:** - Theagenio Cancer Hospital, Thessaloniki, Greece.

**RESUMEN / SUMMARY:** - The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are known to have greater efficacy in EGFR mutation-positive non-small cell lung cancer (NSCLC), although erlotinib also has activity in wild-type disease. We report the successful long-term maintenance treatment of a patient with EGFR wild-type NSCLC with gefitinib and later erlotinib. The patient (male; 44 years old; smoker) was diagnosed with EGFR wild-type NSCLC after computer tomography had revealed a mediastinal mass, and histology and mutation testing had identified the tumor as an EGFR wild-type grade 3 adenocarcinoma. The patient received multiple rounds of chemotherapy, followed by gefitinib maintenance (3 years).

Later on, he received erlotinib maintenance and developed a persistent rash (grade ½) that lasted throughout the treatment. The patient's condition has remained stable on erlotinib for more than 5 years, with no evidence of progression. We describe the patient's disease course and treatment in the context of EGFR TKI therapy and the prognostic factors for long-term clinical outcomes of NSCLC, including the development of erlotinib-induced rash.

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[1030]

**TÍTULO / TITLE:** - Predicting substrates of the human breast cancer resistance protein using a support vector machine method.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Bioinformatics. 2013 Apr 15;14:130. doi: 10.1186/1471-2105-14-130.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2105-14-130](#)

**AUTORES / AUTHORS:** - Hazai E; Hazai I; Ragueneau-Majlessi I; Chung SP; Bikadi Z; Mao Q

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutics, School of Pharmacy, University of Washington, Box 357610, Seattle, Washington 98195, USA. [qmao@u.washington.edu](mailto:qmao@u.washington.edu).

**RESUMEN / SUMMARY:** - BACKGROUND: Human breast cancer resistance protein (BCRP) is an ATP-binding cassette (ABC) efflux transporter that confers multidrug resistance in cancers and also plays an important role in the absorption, distribution and elimination of drugs. Prediction as to if drugs or new molecular entities are BCRP substrates should afford a cost-effective means that can help evaluate the pharmacokinetic properties, efficacy, and safety of these drugs or drug candidates. At present, limited studies have been done to develop in silico prediction models for BCRP substrates. In this study, we developed support vector machine (SVM) models to predict wild-type BCRP substrates based on a total of 263 known BCRP substrates and non-substrates collected from literature. The final SVM model was integrated to a free web server. RESULTS: We showed that the final SVM model had an overall prediction accuracy of ~73% for an independent external validation data set of 40 compounds. The prediction accuracy for wild-type BCRP substrates was ~76%, which is higher than that for non-substrates. The free web server (<http://bcrp.althotas.com>) allows the users to predict whether a query compound is a wild-type BCRP substrate and calculate its physicochemical properties such as molecular weight, logP value, and polarizability. CONCLUSIONS: We have developed an SVM prediction model for wild-type BCRP substrates based on a relatively large number of known wild-type BCRP substrates and non-substrates. This model may prove valuable for screening substrates and non-substrates of BCRP, a clinically important ABC efflux drug transporter.

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[1031]

**TÍTULO / TITLE:** - Hyperthermia enhances mapatumumab-induced apoptotic death through ubiquitin-mediated degradation of cellular FLIP(long) in human colon cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Apr 4;4:e577. doi: 10.1038/cddis.2013.104.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.104](http://1038/cddis.2013.104)

**AUTORES / AUTHORS:** - Song X; Kim SY; Zhou Z; Lagasse E; Kwon YT; Lee YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA.

**RESUMEN / SUMMARY:** - Colorectal cancer is the third leading cause of cancer-related mortality in the world; the main cause of death of colorectal cancer is hepatic metastases, which can be treated with hyperthermia using isolated hepatic perfusion (IHP). In this study, we report that mild hyperthermia potently reduced cellular FLIP(long), (c-FLIP(L)), a major regulator of the death receptor (DR) pathway of apoptosis, thereby enhancing humanized anti-DR4 antibody mapatumumab (Mapa)-mediated mitochondria-independent apoptosis. We observed that overexpression of c-FLIP(L) in CX-1 cells abrogated the synergistic effect of Mapa and hyperthermia, whereas silencing of c-FLIP in CX-1 cells enhanced Mapa-induced apoptosis. Hyperthermia altered c-FLIP(L) protein stability without concomitant reductions in FLIP mRNA. Ubiquitination of c-FLIP(L) was increased by hyperthermia, and proteasome inhibitor MG132 prevented heat-induced downregulation of c-FLIP(L). These results suggest the involvement of the ubiquitin-proteasome system in this process. We also found lysine residue 195 (K195) to be essential for c-FLIP(L) ubiquitination and proteolysis, as mutant c-FLIP(L) lysine 195 arginine (arginine replacing lysine) was left virtually un-ubiquitinated and was refractory to hyperthermia-triggered degradation, and thus partially blocked the synergistic effect of Mapa and hyperthermia. Our observations reveal that hyperthermia transiently reduced c-FLIP(L) by proteolysis linked to K195 ubiquitination, which contributed to the synergistic effect between Mapa and hyperthermia. This study supports the application of hyperthermia combined with other regimens to treat colorectal hepatic metastases.

[1032]

**TÍTULO / TITLE:** - FK-16 Derived from the Anticancer Peptide LL-37 Induces Caspase-Independent Apoptosis and Autophagic Cell Death in Colon Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 20;8(5):e63641. doi: 10.1371/journal.pone.0063641. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063641](http://1371/journal.pone.0063641)

**AUTORES / AUTHORS:** - Ren SX; Shen J; Cheng AS; Lu L; Chan RL; Li ZJ; Wang XJ; Wong CC; Zhang L; Ng SS; Chan FL; Chan FK; Yu J; Sung JJ; Wu WK; Cho CH

**INSTITUCIÓN / INSTITUTION:** - School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China.

**RESUMEN / SUMMARY:** - Host immune peptides, including cathelicidins, have been reported to possess anticancer properties. We previously reported that LL-37, the only cathelicidin in humans, suppresses the development of colon cancer. In this study, the potential anticancer effect of FK-16, a fragment of LL-37 corresponding to residues 17 to 32, on cultured colon cancer cells was evaluated. FK-16 induced a unique pattern of cell death, marked by concurrent activation of caspase-independent apoptosis and autophagy. The former was mediated by the nuclear translocation of AIF and EndoG whereas the latter was characterized by enhanced expression of LC3-I/II, Atg5 and Atg7 and increased formation of LC3-positive autophagosomes. Knockdown of Atg5 or Atg7 attenuated the cytotoxicity of FK-16, indicating FK-16-induced autophagy was pro-death in nature. Mechanistically, FK-16 activated nuclear p53 to upregulate Bax and downregulate Bcl-2. Knockdown of p53, genetic ablation of Bax, or overexpression of Bcl-2 reversed FK-16-induced apoptosis and autophagy. Importantly, abolition of AIF/EndoG-dependent apoptosis enhanced FK-16-induced autophagy while abolition of autophagy augmented FK-16-induced AIF-/EndoG-dependent apoptosis. Collectively, FK-16 induces caspase-independent apoptosis and autophagy through the common p53-Bcl-2/Bax cascade in colon cancer cells. Our study also uncovered previously unknown reciprocal regulation between these two cell death pathways.

[1033]

**TÍTULO / TITLE:** - Apoptosis Effect of Girinimbine Isolated from *Murraya koenigii* on Lung Cancer Cells In Vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:689865. doi: 10.1155/2013/689865. Epub 2013 Mar 13.

●●Enlace al texto completo (gratis o de pago) [1155/2013/689865](#)

**AUTORES / AUTHORS:** - Mohan S; Abdelwahab SI; Cheah SC; Sukari MA; Syam S; Shamsuddin N; Rais Mustafa M

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

**RESUMEN / SUMMARY:** - *Murraya koenigii* Spreng has been traditionally claimed as a remedy for cancer. The current study investigated the anticancer effects of girinimbine, a carbazole alkaloid isolated from *Murraya koenigii* Spreng, on A549 lung cancer cells in relation to apoptotic mechanistic pathway. Girinimbine was isolated from *Murraya koenigii* Spreng. The antiproliferative activity was assayed using MTT and the apoptosis detection was done by annexin V and lysosomal stability assays. Multiparameter cytotoxicity assays were performed

to investigate the change in mitochondrial membrane potential and cytochrome c translocation. ROS, caspase, and human apoptosis proteome profiler assays were done to investigate the apoptotic mechanism of cell death. The MTT assay revealed that the girinimbine induces cell death with an IC50 of 19.01  $\mu$  M. A significant induction of early phase of apoptosis was shown by annexin V and lysosomal stability assays. After 24 h treatment with 19.01  $\mu$  M of girinimbine, decrease in the nuclear area and increase in mitochondrial membrane potential and plasma membrane permeability were readily visible. Moreover the translocation of cytochrome c also was observed. Girinimbine mediates its antiproliferative and apoptotic effects through up- and downregulation of apoptotic and antiapoptotic proteins. There was a significant involvement of both intrinsic and extrinsic pathways. Moreover, the upregulation of p53 as well as the cell proliferation repressor proteins, p27 and p21, and the significant role of insulin/IGF-1 signaling were also identified. Moreover the caspases 3 and 8 were found to be significantly activated. Our results taken together indicated that girinimbine may be a potential agent for anticancer drug development.

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[1034]

**TÍTULO / TITLE:** - Effect of Botulinum Toxin A on Proliferation and Apoptosis in the T47D Breast Cancer Cell Line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(2):891-4.

**AUTORES / AUTHORS:** - Bandala C; Perez-Santos JL; Lara-Padilla E; Delgado Lopez G; Anaya-Ruiz M

**INSTITUCIÓN / INSTITUTION:** - Department of Research Support, Instituto Nacional de Rehabilitacion, Mexico City, Mexico E-mail : [manaya19@yahoo.com.mx](mailto:manaya19@yahoo.com.mx).

**RESUMEN / SUMMARY:** - The present study was performed to assess the activity of the botulinum toxin A on breast cancer cells. The T47D cell line was exposed to diverse concentrations of the botulinum toxin A and cell viability and apoptosis were estimated using MTT and propidium iodine/annexin V methods, respectively. Botulinum toxin A exerted greater cytotoxic activity in T47D cells in comparison with MCF10A normal cells; this appeared to be via apoptotic processes caspase-3 and -7. In conclusion, botulinum toxin A induces caspase-3 and -7 dependent apoptotic processes in the T47D breast cancer cell line.

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[1035]

**TÍTULO / TITLE:** - DNA-Bound Platinum Is the Major Determinant of Cisplatin Sensitivity in Head and Neck Squamous Carcinoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 17;8(4):e61555. doi: 10.1371/journal.pone.0061555. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061555](https://doi.org/10.1371/journal.pone.0061555)

**AUTORES / AUTHORS:** - Martens-de Kemp SR; Dalm SU; Wijnolts FM; Brink A; Honeywell RJ; Peters GJ; Braakhuis BJ; Brakenhoff RH

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology/Head-Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands.

**RESUMEN / SUMMARY:** - **PURPOSE:** The combination of systemic cisplatin with local and regional radiotherapy as primary treatment of head and neck squamous cell carcinoma (HNSCC) leads to cure in approximately half of the patients. The addition of cisplatin has significant effects on outcome, but despite extensive research the mechanism underlying cisplatin response is still not well understood. **METHODS:** We examined 19 HNSCC cell lines with variable cisplatin sensitivity. We determined the TP53 mutational status of each cell line and investigated the expression levels of 11 potentially relevant genes by quantitative real-time PCR. In addition, we measured cisplatin accumulation and retention, as well as the level of platinum-DNA adducts. **RESULTS:** We found that the IC50 value was significantly correlated with the platinum-DNA adduct levels that accumulated during four hours of cisplatin incubation ( $p = 0.002$ ). We could not find a significant correlation between cisplatin sensitivity and any of the other parameters tested, including the expression levels of established cisplatin influx and efflux transporters. Furthermore, adduct accumulation did not correlate with mRNA expression of the investigated influx pumps (CTR1 and OCT3) nor with that of the examined DNA repair genes (ATR, ATM, BRCA1, BRCA2 and ERCC1). **CONCLUSION:** Our findings suggest that the cisplatin-DNA adduct level is the most important determinant of cisplatin sensitivity in HNSCC cells. Imaging with radio-labeled cisplatin might have major associations with outcome.

[1036]

**TÍTULO / TITLE:** - Cidofovir selectivity is based on the different response of normal and cancer cells to DNA damage.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Med Genomics. 2013 May 23;6(1):18.

●●Enlace al texto completo (gratis o de pago) [1186/1755-8794-6-18](https://doi.org/10.1186/1755-8794-6-18)

**AUTORES / AUTHORS:** - De Schutter T; Andrei G; Topalis D; Naesens L; Snoeck R

**RESUMEN / SUMMARY:** - **BACKGROUND:** Cidofovir (CDV) proved efficacious in treatment of human papillomaviruses (HPVs) hyperplasias. Antiproliferative effects of CDV have been associated with apoptosis induction, S-phase accumulation, and increased levels of tumor suppressor proteins. However, the molecular mechanisms for the selectivity and antitumor activity of CDV against HPV-transformed cells remain unexplained. **METHODS:** We evaluated CDV drug metabolism and incorporation into cellular DNA, in addition to whole genome gene expression profiling by means of microarrays in two HPV+

cervical carcinoma cells, HPV- immortalized keratinocytes, and normal keratinocytes. RESULTS: Determination of the metabolism and drug incorporation of CDV into genomic DNA demonstrated a higher rate of drug incorporation in HPV+ tumor cells and immortalized keratinocytes compared to normal keratinocytes. Gene expression profiling clearly showed distinct and specific drug effects in the cell types investigated. Although an effect on inflammatory response was seen in all cell types, different pathways were identified in normal keratinocytes compared to immortalized keratinocytes and HPV+ tumor cells. Notably, Rho GTPase pathways, LXR/RXR pathways, and acute phase response signaling were exclusively activated in immortalized cells. CDV exposed normal keratinocytes displayed activated cell cycle regulation upon DNA damage signaling to allow DNA repair via homologous recombination, resulting in genomic stability and survival. Although CDV induced cell cycle arrest in HPV- immortalized cells, DNA repair was not activated in these cells. In contrast, HPV+ cells lacked cell cycle regulation, leading to genomic instability and eventually apoptosis. CONCLUSIONS: Taken together, our data provide novel insights into the mechanism of action of CDV and its selectivity for HPV-transformed cells. The proposed mechanism suggests that this selectivity is based on the inability of HPV+ cells to respond to DNA damage, rather than on a direct anti-HPV effect. Since cell cycle control is deregulated by the viral oncoproteins E6 and E7 in HPV+ cells, these cells are more susceptible to DNA damage than normal keratinocytes. Our findings underline the therapeutic potential of CDV for HPV-associated malignancies as well as other neoplasias.

[1037]

**TÍTULO / TITLE:** - Targeted therapy of the XIAP/proteasome pathway overcomes TRAIL-resistance in carcinoma by switching apoptosis signaling to a Bax/Bak-independent 'type I' mode.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 May 23;4:e643. doi: 10.1038/cddis.2013.67.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.67](http://1038/cddis.2013.67)

**AUTORES / AUTHORS:** - Gillissen B; Richter A; Richter A; Overkamp T; Essmann F; Hemmati PG; Preissner R; Belka C; Daniel PT

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Oncology and Tumor Immunology, University Medical Center Charite, Campus Berlin-Buch, Humboldt University, Berlin, Germany.

**RESUMEN / SUMMARY:** - TRAIL is a promising anticancer agent, capable of inducing apoptosis in a wide range of treatment-resistant tumor cells. In 'type II' cells, the death signal triggered by TRAIL requires amplification via the mitochondrial apoptosis pathway. Consequently, deregulation of the intrinsic apoptosis-signaling pathway, for example, by loss of Bax and Bak, confers TRAIL-resistance and limits its application. Here, we show that despite

resistance of Bax/Bak double-deficient cells, TRAIL-treatment resulted in caspase-8 activation and complete processing of the caspase-3 proenzymes. However, active caspase-3 was degraded by the proteasome and not detectable unless the XIAP/proteasome pathway was inhibited. Direct or indirect inhibition of XIAP by RNAi, Mithramycin A or by the SMAC mimetic LBW-242 as well as inhibition of the proteasome by Bortezomib overcomes TRAIL-resistance of Bax/Bak double-deficient tumor cells. Moreover, activation and stabilization of caspase-3 becomes independent of mitochondrial death signaling, demonstrating that inhibition of the XIAP/proteasome pathway overcomes resistance by converting 'type II' to 'type I' cells. Our results further demonstrate that the E3 ubiquitin ligase XIAP is a gatekeeper critical for the 'type II' phenotype. Pharmacological manipulation of XIAP therefore is a promising strategy to sensitize cells for TRAIL and to overcome TRAIL-resistance in case of central defects in the intrinsic apoptosis-signaling pathway.

[1038]

**TÍTULO / TITLE:** - Proteomic Identification of Neoadjuvant Chemotherapy-Related Proteins in Bulky Stage IB-IIA Squamous Cervical Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Reprod Sci.* 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago)

[1177/1933719113485291](#)

**AUTORES / AUTHORS:** - Zou S; Shen Q; Hua Y; Jiang W; Zhang W; Zhu X

**INSTITUCIÓN / INSTITUTION:** - 1Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Wenzhou Medical College, Wenzhou, China.

**RESUMEN / SUMMARY:** - Objective:The aim of this study was to investigate the effect of neoadjuvant chemotherapy (NAC) on the human squamous cervical cancer using proteomics profiling and to obtain related proteins to NAC exposure and response.Methods:Paired samples of early-stage bulky squamous cervical cancer before and after NAC treatment from patients who responded to NAC were obtained and submitted to 2-dimensional gel electrophoresis and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MS). The expression and localization of the interesting proteins in additional paired samples were confirmed by Western blot analysis and immunohistochemistry.Results:The comparison of the proteins present before and after NAC revealed that 116 protein spots were significantly changed. In all, 31 proteins were analyzed by MS, and 15 proteins were upregulated in the cancer tissue after NAC relative to the level before NAC, whereas 16 proteins were downregulated after NAC. The significantly higher expression of peroxiredoxin 1 and significantly lower expression of galectin 1 after NAC treatment were confirmed by Western blot.Conclusions:Proteomics can be used to identify the NAC-related proteins in squamous cervical cancer.

The change in proteins may be associated with NAC exposure and response, but insight into their relevance requires further study.

[1039]

**TÍTULO / TITLE:** - Targeting PI3K/Akt represses Hypoxia inducible factor-1alpha activation and sensitizes Rhabdomyosarcoma and Ewing's sarcoma cells for apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Cell Int. 2013 Apr 16;13(1):36.

●●Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-36](#)

**AUTORES / AUTHORS:** - Kilic-Eren M; Boylu T; Tabor V

**RESUMEN / SUMMARY:** - BACKGROUND: Hypoxia inducible factor alpha (HIF-1alpha) has been identified as an important novel target in apoptosis resistance of pediatric tumors such as Rhabdomyosarcoma (RMS) and Ewing's sarcoma (ES). Evidence suggests that PI3K/Akt signaling plays a role in regulation of HIF-1alpha activation as well as apoptosis resistance in various adult tumors. However the relevance of PI3K/Akt signaling in HIF-1alpha activation and apoptosis resistance in childhood tumors has not been addressed yet. Thus, this study was to investigate whether PI3K/Akt signaling is involved in hypoxia induced activation of HIF-1alpha as well as in resistance to hypoxia-induced apoptosis in childhood tumors such as RMS and ES. METHODS: Constitutive activation of PI3K/Akt signaling was analyzed by Western blotting. Hypoxic activation of HIF-1alpha was determined by Western Blot analysis and electrophoretic mobility shift assay. Apoptosis was determined by flow cytometric analysis of the propidium iodine stained nuclei of cells treated with PI3K inhibitor LY294002 in combination with either TNF-related apoptosis-inducing ligand (TRAIL) or doxorubicin. RESULTS: This study demonstrated that PI3K/Akt signaling was constitutively activated in RMS and ES cell lines, A204 and A673, respectively. Targeting PI3K/Akt signaling by the inhibitor LY294002 (30 muM) significantly decreased the protein expression as well as DNA binding activity of HIF-1alpha and restored the apoptosis-inducing ability of cells in hypoxia. Additionally, pretreatment with LY294002 sensitized A204 and A673 cells to TRAIL or doxorubicin induced apoptosis under hypoxia. CONCLUSION: These results suggest that the constitutively active PI3K/Akt signaling contributes to hypoxic activation of HIF-1alpha as well as HIF1alpha-mediated apoptosis resistance in RMS and ES cells under hypoxia.

[1040]

**TÍTULO / TITLE:** - Telomere-Homologous G-Rich Oligonucleotides Sensitize Human Ovarian Cancer Cells to TRAIL-Induced Growth Inhibition and Apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nucleic Acid Ther. 2013 Jun;23(3):167-74. doi: 10.1089/nat.2012.0401. Epub 2013 May 2.

●●Enlace al texto completo (gratis o de pago) [1089/nat.2012.0401](#)

**AUTORES / AUTHORS:** - Sarkar S; Faller DV

**INSTITUCIÓN / INSTITUTION:** - 1 Cancer Center, Boston University School of Medicine, Boston, Massachusetts.

**RESUMEN / SUMMARY:** - G-rich T-oligos (GT-oligos; oligonucleotides with homology to telomeres) elicit a DNA damage response in cells and induce cytotoxic effects in certain tumor cell lines. We have previously shown that GT-oligo inhibits growth, arrests cell cycle, and induces apoptosis in ovarian, pancreatic, and prostate cancer cells. However, not all ovarian cancer cell lines are susceptible to GT-oligo exposure. GT-oligo was found to induce transcript expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors DR-4 and DR-5, which are generally silenced in ovarian cancer cells, rendering them insensitive to TRAIL. Exposure of TRAIL- and GT-oligo-resistant cell lines to GT-oligo rendered them sensitive to the cytotoxic effects of TRAIL, producing more than additive inhibition of growth. An intracellular inhibitor of the extrinsic apoptotic pathway, FLICE-like Inhibitory Protein-Short (FLIPs), was down-regulated and Jun kinase (JNK) was activated by exposure to GT-oligo. JNK inhibition partially reversed the growth inhibition caused by the combination of GT-oligo and TRAIL indicating partial involvement of the Jun kinase pathway in the resulting cytotoxic effect. Both caspase-8 and caspases 3/7 were activated by exposure to GT-oligo plus TRAIL, consistent with activation of the extrinsic apoptotic pathway. These results demonstrate a novel way of sensitizing resistant ovarian cancer cells to TRAIL-mediated cytotoxicity.

[1041]

**TÍTULO / TITLE:** - The epimer of kaurenoic acid from *Croton antisiphiliticus* is cytotoxic toward B-16 and HeLa tumor cells through apoptosis induction.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Res. 2013 Apr 2;12(2):1005-11. doi: 10.4238/2013.April.2.16.

●●Enlace al texto completo (gratis o de pago) [4238/2013.April.2.16](#)

**AUTORES / AUTHORS:** - Fernandes VC; Pereira SI; Coppede J; Martins JS; Rizo WF; Belebony RO; Marins M; Pereira PS; Pereira AM; Fachin AL

**INSTITUCIÓN / INSTITUTION:** - Unidade de Biotecnologia, Universidade de Ribeirão Preto, Ribeirão Preto, SP, Brasil.

**RESUMEN / SUMMARY:** - Cancer has become the leading cause of death in developing countries due to increased life expectancy of the population and changes in lifestyle. Studies on active principles of plants have motivated researchers to develop new antitumor agents that are specific and effective for treatment of neoplasms. Kaurane diterpenes are considered important compounds in the development of new and highly effective anticancer chemotherapeutic agents due to their cytotoxic properties in the induction of apoptosis. We evaluated the cytotoxic and apoptotic activity of the epimer of

kaurenoic acid (EKA) isolated from the medicinal plant *Croton antisiphiliticus* (Euphorbiaceae) toward tumor cell lines HeLa and B-16 and normal fibroblasts 3T3. Based on analyses with the MTT test, EKA showed cytotoxic activity, with half maximal inhibitory concentration values of 59.41, 68.18 and 60.30 microg/mL for the B-16, HeLa and 3T3 cell lines, respectively. The assay for necrotic or apoptotic cells by differential staining showed induction of apoptosis in all three cell lines. We conclude that EKA is not selective between tumor and normal cell lines; the mechanism of action of EKA is induction of apoptosis, which is part of the innate mechanism of cell defense against neoplasia.

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[1042]

**TÍTULO / TITLE:** - Crude alkaloid extract of *Rhazya stricta* inhibits cell growth and sensitizes human lung cancer cells to cisplatin through induction of apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Biol. 2013 Mar;36(1):12-21. doi: 10.1590/S1415-47572013005000009. Epub 2013 Mar 4.

●●Enlace al texto completo (gratis o de pago) [1590/S1415-47572013005000009](#)

**AUTORES / AUTHORS:** - Elkady AI

**INSTITUCIÓN / INSTITUTION:** - Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

**RESUMEN / SUMMARY:** - There is an urgent need to improve the clinical management of non-small cell lung cancer (NSCLC), one of the most frequent causes of cancer-related deaths in men and women worldwide. *Rhazya stricta*, an important medicinal plant used in traditional Oriental medicine, possesses anti-oxidant, anti-carcinogenic and free radical scavenging properties. This study was done to explore the potential anticancer activity of a crude alkaloid extract of *R. stricta* (CAERS) against the NSCLC line A549. CAERS markedly suppressed the growth of A549 cells and considerably enhanced the anti-proliferative potential of cisplatin. CAERS-mediated inhibition of A549 cell growth correlated with the induction of apoptosis that was accompanied by numerous morphological changes, DNA fragmentation, an increase in the Bax/Bcl-2 ratio, the release of mitochondrial cytochrome c, activation of caspases 3 and 9 and cleavage of poly(ADP-ribose)-polymerase. CAERS reduced the constitutive expression of anti-apoptotic proteins (Bcl-2, Bcl-XL, Mcl-1 and Survivin) and cell cycle regulating proteins (cyclin D1 and c-Myc), but enhanced expression of the proapoptotic proteins Noxa and BAD. These observations indicate that CAERS induced apoptosis and sensitized NSCLC to cisplatin via a mitochondria-mediated apoptotic pathway. These data provide a rationale for using a combination of CAERS and CDDP to treat NSCLC and other CDDP-resistant tumors.

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[1043]

**TÍTULO / TITLE:** - Spongiatriol inhibits nuclear factor kappa B activation and induces apoptosis in pancreatic cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mar Drugs. 2013 Apr 2;11(4):1140-51. doi: 10.3390/md11041140.

●●Enlace al texto completo (gratis o de pago) [3390/md11041140](#)

**AUTORES / AUTHORS:** - Guzman E; Maher M; Temkin A; Pitts T; Wright A

**INSTITUCIÓN / INSTITUTION:** - Center for Marine Biomedical and Biotechnology Research, Harbor Branch Oceanographic Institute at Florida Atlantic University, 5600 US 1 North, Fort Pierce, FL 34946, USA. [eguzman9@hboi.fau.edu](mailto:eguzman9@hboi.fau.edu).

**RESUMEN / SUMMARY:** - Pancreatic cancer, the fourth leading cause of cancer death in the US, is highly resistant to all current chemotherapies, and its growth is facilitated by chronic inflammation. The majority of pro-inflammatory cytokines initiate signaling cascades that converge at the activation of the Nuclear Factor Kappa B (NFkappaB), a signal transduction molecule that promotes cell survival, proliferation and angiogenesis. In an effort to identify novel inhibitors of NFkappaB, the HBOI library of pure compounds was screened using a reporter cell line that produces luciferin under the transcriptional control of NFkappaB. Seven compounds were identified through this screen, but in the case of five of them, their reported mechanism of action made them unlikely to be specific NFkappaB inhibitors. Spongiatriol, a marine furanoditerpenoid that was first isolated in the 1970s, is shown here to inhibit NFkappaB transcriptional activity in a reporter cell line, to reduce levels of phosphorylated (active) NFkappaB in the AsPC-1 cell line, to have an IC50 for cytotoxicity in the low micromolar range against the AsPC-1, BxPC-3, MiaPaCa-2 and Panc-1 pancreatic cancer cell lines, and to induce moderate but significant apoptosis in both the AsPC-1 and the Panc-1 cell lines.

[1044]

**TÍTULO / TITLE:** - Celastrol induces apoptosis of gastric cancer cells by miR-146a inhibition of NF-kappaB activity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Cell Int. 2013 May 27;13(1):50. doi: 10.1186/1475-2867-13-50.

●●Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-50](#)

**AUTORES / AUTHORS:** - Sha M; Ye J; Zhang LX; Luan ZY; Chen YB

**INSTITUCIÓN / INSTITUTION:** - Institute of Clinical medicine, Taizhou people's Hospital affiliated of Nantong University of medicine, 210 Yingchun, Taizhou, Jiangsu Province, 225300, China. [tzrmyy5211@163.com](mailto:tzrmyy5211@163.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Celastrol, a plant triterpene, is known to play important role in inhibiting proliferation and inducing apoptosis of gastric cancer cells. In the present study, the mechanism of celastrol on gastric cancer cells apoptosis was examined. METHODS: We assessed effect of celastrol on NF-kappaB signaling pathway in gastric cancer cells using western blot and

luciferase reporter assay. The real-time PCR was used to evaluate the effect of celastrol on miR-146a expression, and miR-146a mimic to evaluate whether over-expression of miR-146a can affect NF-kappaB activity. Finally, the effect of miR-146a on celastrol-induced anti-tumor activity was assessed using miR-146a inhibitor. RESULTS: Celastrol decreased gastric cancer cells viability in a dose-dependent. Celastrol also reduced I kappa B phosphorylation, nuclear P65 protein levels and NF-kappaB activity. Furthermore, Celastrol could increase miR-146a expression and up-regulation of miR-146a expression could suppress NF-kappaB activity. More important, down-regulation of miR-146a expression can reverse the effect of celastrol on NF-kappaB activity and apoptosis in gastric cancer cells. CONCLUSIONS: In this study, we demonstrated that the effect of celastrol on apoptosis is due to miR-146a inhibition of NF-kappaB activity.

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[1045]

**TÍTULO / TITLE:** - Tetrandrine triggers apoptosis and cell cycle arrest in human renal cell carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Nat Med. 2013 Apr 6.

●●Enlace al texto completo (gratis o de pago) [1007/s11418-013-0765-](#)

[0](#)

**AUTORES / AUTHORS:** - Chen T; Ji B; Chen Y

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, The Affiliated Hospital of Medical College Qingdao University, Qingdao, People's Republic of China.

**RESUMEN / SUMMARY:** - Tetrandrine is a cytotoxic compound capable of exerting remarkable antitumor activity against many cancer cells in vitro and in vivo. However, little is known about its effect on human renal cell carcinoma (RCC). In the present study, using RCC 786-O, 769-P and ACHN cell lines as the model system, we demonstrated the anticancer effect of tetrandrine against RCC and clarified its underlying mechanisms. Tetrandrine treatment showed growth inhibitory effects on RCC cells in a time- and dose-dependent manner. Additionally, flow cytometric studies revealed that tetrandrine was capable of inducing G1 cell cycle arrest and apoptosis in RCC cells. Mechanically, activation of caspase-8, caspase-9, and caspase-3 and increasing expression of cell cycle regulatory protein p21WAF1/CIP1 and p27KIP1 were observed in tetrandrine-treated RCC cells. This study provides the first evidence that tetrandrine triggered apoptosis and cell cycle arrest in RCC 786-O, 769-P and ACHN cells in vitro; these events are associated with caspase cascade activation and upregulation of p21 and p27. Our results thus provide rational evidence supporting the application of tetrandrine as a novel therapeutic agent against RCC in the clinical setting.

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[1046]

**TÍTULO / TITLE:** - M-ds-P21 induces cell apoptosis in bladder cancer T24 cells through P53 independent pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer Res Ther. 2013 Jan-Mar;9(1):54-9. doi: 10.4103/0973-1482.110367.

●●Enlace al texto completo (gratis o de pago) [4103/0973-1482.110367](#)

**AUTORES / AUTHORS:** - Wang H; Liu W; Jin J; Zhou L; Liang L; Guo Y

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Peking University First Hospital and Institute of Urology, Peking University, National Research Center for Genitourinary Oncology, Beijing, China.

**RESUMEN / SUMMARY:** - OBJECTIVES: To investigate the effect of M-ds-P21 on the apoptosis of bladder cancer T24 cells and its potential mechanism. MATERIALS AND METHODS: Effect of M-ds-P21 on T24 cells were assessed by cell morphology and Western blot. Apoptosis was quantified by Annexin-V flow-cytometry analysis. To uncover the role of P53 in M-ds-P21-mediated apoptosis of T24 cells, we knocked down P53 before treating cells with M-ds-P21, and then assayed P21 and apoptosis-related protein by Western blot. To uncover the mechanism by which M-ds-P21 played stronger effect than ds-P21, we performed confocal microscope analyses. RESULTS: Both M-ds-P21 and ds-P21 treatment changed the cell morphology, leading to cell apoptosis after 3 days. Apoptosis induced by M-ds-P21 and ds-P21 treatment is not P53-dependent but caspase-dependent. Compared with ds-P21, M-ds-P21 significantly increased the bioavailability of ds-RNA in T24 cells. CONCLUSIONS: M-ds-P21 treatment induces more apoptotic population than ds-P21 does. The mechanism for stronger effect of M-ds-P21 is partly due to the enhanced bioavailability of ds-RNA in human bladder cancer T24 cells, and not P53-dependent but caspase-dependent.

[1047]

**TÍTULO / TITLE:** - Dipsacus asperoides polysaccharide induces apoptosis in osteosarcoma cells by modulating the PI3K/Akt pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carbohydr Polym. 2013 Jun 20;95(2):780-4. doi: 10.1016/j.carbpol.2013.03.009. Epub 2013 Mar 13.

●●Enlace al texto completo (gratis o de pago)

[1016/j.carbpol.2013.03.009](#)

**AUTORES / AUTHORS:** - Chen J; Yao D; Yuan H; Zhang S; Tian J; Guo W; Liang W; Li H; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - Institute of Osteosarcoma, Tangdu Hospital, The Fourth Military Medical University, Xi'an, 710038, China.

**RESUMEN / SUMMARY:** - An alkaline extractable and water-soluble polysaccharide (ADAPW), with an average molecular weight of 16kDa, was purified from the alkaline extraction of the roots of Dipsacus asperoides. Monosaccharide component analysis indicated that ADAPW was composed of

glucose, rhamnose, arabinose and mannose in a molar ratio of 8.54:1.83:1.04:0.42. This study aimed to investigate the effect of ADAPW on the viability of human osteosarcoma cell line HOS cells, and explore the possible mechanisms. The results revealed that ADAPW inhibited the proliferation of HOS cells in a dose-dependent manner by inducing apoptosis. Furthermore, treatment with ADAPW caused a loss of mitochondrial membrane potential and accumulation of reactive oxygen species (ROS). In addition, Western blot analysis demonstrated that ADAPW down-regulated the protein expressions of PI3K and phosphorylated Akt (pAkt) in HOS cells. Taken together, induction of apoptosis on HOS cells by ADAPW was mainly associated with ROS production, mitochondrial dysfunction, and inhibition of PI3K/Akt signaling pathway. So this finding suggests that ADAPW may be potentially effective in cancer prevention against human osteosarcoma.

[1048]

**TÍTULO / TITLE:** - Salinomycin inhibits Akt/NF-kappaB and induces apoptosis in cisplatin resistant ovarian cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Epidemiol. 2013 Mar 28. pii: S1877-7821(13)00031-3. doi: 10.1016/j.canep.2013.02.008.

●●Enlace al texto completo (gratis o de pago)

[1016/j.canep.2013.02.008](http://1016/j.canep.2013.02.008)

**AUTORES / AUTHORS:** - Parajuli B; Lee HG; Kwon SH; Cha SD; Shin SJ; Lee GH; Bae I; Cho CH

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Keimyung University, School of Medicine, Daegu, Republic of Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Despite advances in treatment, ovarian cancer is the most lethal gynecologic malignancy. Therefore significant efforts are being made to develop novel strategies for the treatment of ovarian cancer. Salinomycin has been shown to be highly effective in the elimination of cancer stem cells both in vitro and in vivo. The present study focused on investigating important cell signaling molecules such as Akt and NF-kappaB during salinomycin-induced apoptosis in cisplatin resistant ovarian cancer cells (A2780cis). METHODS: MTT assay was performed to determine cell viability. Flow cytometry and DNA fragmentation assay were performed to analyze the effect on cell cycle and apoptosis. The expression of apoptosis related proteins was evaluated by Western blot analysis. RESULTS: The cell viability was significantly reduced by salinomycin treatment in a dose dependent manner. The flow cytometry result showed an increase in sub-G1 phase. Salinomycin inhibited the nuclear transportation of NF-kappaB, and downregulated Akt expression. Declined Bcl-2, activation of caspase-3 and increased PARP cleavage triggered apoptosis. Moreover, DNA fragmentation assay also revealed apoptotic induction. CONCLUSION: The result suggested that salinomycin-induced apoptosis in A2780cis was associated with inhibition of

Akt/NF-kappaB. It may become a potential chemotherapeutic agent for the cisplatin resistant ovarian cancer therapy.

[1049]

**TÍTULO / TITLE:** - Polyphenols Isolated from Propolis Augment TRAIL-Induced Apoptosis in Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:731940. doi: 10.1155/2013/731940. Epub 2013 Mar 19.

●●Enlace al texto completo (gratis o de pago) [1155/2013/731940](#)

**AUTORES / AUTHORS:** - Szliszka E; Krol W

**INSTITUCIÓN / INSTITUTION:** - Department of Microbiology and Immunology, Medical University of Silesia in Katowice, Jordana 19, 41 808 Zabrze, Poland.

**RESUMEN / SUMMARY:** - Epidemiological data support the concept that phenols and polyphenols in diet are safe and nontoxic, and have long-lasting beneficial effects on human health. The potential target for complementary and alternative medicine (CAM) research has been on the discovery of natural compounds that can be used in the prevention and treatment of cancer. Propolis is one of the richest sources of plant phenolics (flavonoids and phenolic acids). The ethanolic extract of propolis (EEP) and its polyphenols possess immunomodulatory, chemopreventive, and antitumor effects. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a naturally occurring anticancer agent that preferentially induces apoptosis in cancer cells and is not toxic to normal cells. Endogenous TRAIL plays a significant role in immunosurveillance and defense against cancer cells. However, as more tumor cells are reported to be resistant to TRAIL-mediated death, it is important to develop new strategies to overcome this resistance. EEP and polyphenols isolated from propolis have been shown to sensitize cancer cells to TRAIL-induced apoptosis. In this paper we demonstrate for the first time the crucial role of the main phenolics isolated from propolis in enhancing TRAIL-mediated death in tumor cells for cancer chemoprevention.

[1050]

**TÍTULO / TITLE:** - Anticancer activity and mediation of apoptosis in human HL-60 leukaemia cells by edible sea cucumber (*Holothuria edulis*) extract.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Food Chem. 2013 Aug 15;139(1-4):326-31. doi: 10.1016/j.foodchem.2013.01.058. Epub 2013 Feb 4.

●●Enlace al texto completo (gratis o de pago)

[1016/j.foodchem.2013.01.058](#)

**AUTORES / AUTHORS:** - Wijesinghe WA; Jeon YJ; Ramasamy P; Wahid ME; Vairappan CS

**INSTITUCIÓN / INSTITUTION:** - School of Marine Biomedical Sciences, Jeju National University, Jeju 690-756, Republic of Korea.

**RESUMEN / SUMMARY:** - Sea cucumbers have been a dietary delicacy and important ingredient in Asian traditional medicinal over many centuries. In this study, edible sea cucumber *Holothuria edulis* was evaluated for its in vitro anticancer potential. An aqueous fraction of the edible sea cucumber (ESC-AQ) has been shown to deliver a strong cytotoxic effect against the human HL-60 leukaemia cell line. An induction effect of apoptotic body formation in response to ESC-AQ treatment was confirmed in HL-60 cells stained with Hoechst 33342 and confirmed via flow cytometry analysis. The up regulation of Bax and caspase-3 protein expression was observed while the expression of Bcl-xL protein was down regulated in ESC-AQ treated HL-60 cells. Due to the profound anticancer activity, ESC-AQ appears to be an economically important biomass fraction that can be exploited in numerous industrial applications as a source of functional ingredients.

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[1051]

**TÍTULO / TITLE:** - miR-146a inhibits cell growth, cell migration and induces apoptosis in non-small cell lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e60317. doi: 10.1371/journal.pone.0060317. Epub 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060317](http://1371/journal.pone.0060317)

**AUTORES / AUTHORS:** - Chen G; Umelo IA; Lv S; Teugels E; Fostier K; Kronenberger P; Dewaele A; Sadones J; Geers C; De Greve J

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People's Republic of China.

**RESUMEN / SUMMARY:** - Aberrant expression of microRNA-146a (miR-146a) has been reported to be involved in the development and progression of various types of cancers. However, its role in non-small cell lung cancer (NSCLC) has not been elucidated. The aim of this study was to investigate the contribution of miR-146a to various aspects of the malignant phenotype of human NSCLCs. In functional experiments, miR-146a suppressed cell growth, induced cellular apoptosis and inhibited EGFR downstream signaling in five NSCLC cell lines (H358, H1650, H1975, HCC827 and H292). miR-146a also inhibited the migratory capacity of these NSCLC cells. On the other hand, miR-146a enhanced the inhibition of cell proliferation by drugs targeting EGFR, including both TKIs (gefitinib, erlotinib, and afatinib) and a monoclonal antibody (cetuximab). These effects were independent of the EGFR mutation status (wild type, sensitizing mutation or resistance mutation), but were less potent compared to the effects of siRNA targeting of EGFR. Our results suggest that these effects of miR-146a are due to its targeting of EGFR and NF-kappaB signaling. We also found, in clinical formalin fixed paraffin embedded (FFPE) lung cancer samples, that low expression of miR-146a was correlated with advanced clinical TNM stages and distant metastasis in NSCLC (P<0.05). The

patients with high miR-146a expression in their tumors showed longer progression-free survival (25.6 weeks in miR-146a high patients vs. 4.8 weeks in miR-146a low patients,  $P < 0.05$ ). miR-146a is therefore a strong candidate prognostic biomarker in NSCLC. Thus inducing miR-146a might be a therapeutic strategy for NSCLC.

[1052]

**TÍTULO / TITLE:** - Synergistic anticancer effect of the extracts from *Polyalthia evecata* caused apoptosis in human hepatoma (HepG2) cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Trop Biomed. 2012 Aug;2(8):589-96. doi: 10.1016/S2221-1691(12)60103-8.

●●Enlace al texto completo (gratis o de pago) [1016/S2221-1691\(12\)60103-8](#)

**AUTORES / AUTHORS:** - Machana S; Weerapreeyakul N; Barusrux S; Thumanu K; Tanthanuch W

**INSTITUCIÓN / INSTITUTION:** - Graduate School, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, 40002, Thailand.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To evaluate the anticancer activity of the extract fraction of *Polyalthia evecata* (*P. evecata*) (Pierre) Finet & Gagnep and the synergistic anticancer effect of the extracts from *P. evecata* by using the ATR/FT-IR spectroscopy. **METHODS:** The 50% ethanol-water crude leaf extract of *P. evecata* (EW-L) was prepared and was further fractionated to isolate various fractions. The anticancer activity was investigated from cytotoxicity against HepG2 using a neutral red assay and apoptosis induction by evaluation of nuclei morphological changes after DAPI staining. Synergistic anticancer effects of the extracts from *P. evecata* were performed using the ATR/FT-IR spectroscopy. **RESULTS:** The result showed that the EW-L showed higher cytotoxicity and apoptosis induction in HepG2 cells than its fractionated extracts. The hexane extract exhibited higher cytotoxicity and apoptosis induction than the water extracts, but less than the EW-L. The combined water and hexane extracts apparently increased cytotoxicity and apoptosis induction. The %apoptotic cells induced by the extract mixture were increased about 2-fold compared to the single hexane extract. **CONCLUSIONS:** The polar extract fraction is necessary for the anticancer activity of the non-polar extract fraction. The ATR/FT-IR spectra illustrates the physical interaction among the constituents in the extract mixture and reveals the presence of polyphenolic constituents in the EW-L, which might play a role for the synergistic anticancer effect.

[1053]

**TÍTULO / TITLE:** - Novel monofunctional platinum (II) complex Mono-Pt induces apoptosis-independent autophagic cell death in human ovarian carcinoma cells, distinct from cisplatin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Autophagy. 2013 Apr 11;9(7).

**AUTORES / AUTHORS:** - Guo WJ; Zhang YM; Zhang L; Huang B; Tao FF; Chen W; Guo ZJ; Xu Q; Sun Y

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Pharmaceutical Biotechnology; School of Life Sciences; Nanjing University; Nanjing, China.

**RESUMEN / SUMMARY:** - Failure to engage apoptosis appears to be a leading mechanism of resistance to traditional platinum drugs in patients with ovarian cancer. Therefore, an alternative strategy to induce cell death is needed for the chemotherapy of this apoptosis-resistant cancer. Here we report that autophagic cell death, distinct from cisplatin-induced apoptosis, is triggered by a novel monofunctional platinum (II) complex named Mono-Pt in human ovarian carcinoma cells. Mono-Pt-induced cell death has the following features: cytoplasmic vacuolation, caspase-independent, no nuclear fragmentation or chromatin condensation, and no apoptotic bodies. These characteristics integrally indicated that Mono-Pt, rather than cisplatin, initiated a nonapoptotic cell death in Caov-3 ovarian carcinoma cells. Furthermore, incubation of the cells with Mono-Pt but not with cisplatin produced an increasing punctate distribution of microtubule-associated protein 1 light chain 3 (LC3), and an increasing ratio of LC3-II to LC3-I. Mono-Pt also caused the formation of autophagic vacuoles as revealed by monodansylcadaverine staining and transmission electron microscopy. In addition, Mono-Pt-induced cell death was significantly inhibited by the knockdown of either BECN1 or ATG7 gene expression, or by autophagy inhibitors 3-methyladenine, chloroquine and bafilomycin A 1. Moreover, the effect of Mono-Pt involved the AKT1-MTOR-RPS6KB1 pathway and MAPK1 (ERK2)/MAPK3 (ERK1) signaling, since the MTOR inhibitor rapamycin increased, while the MAPK1/3 inhibitor U0126 decreased Mono-Pt-induced autophagic cell death. Taken together, our results suggest that Mono-Pt exerts anticancer effect via autophagic cell death in apoptosis-resistant ovarian cancer. These findings lead to increased options for anticancer platinum drugs to induce cell death in cancer.

[1054]

**TÍTULO / TITLE:** - Upregulation of miR-150\* and miR-630 Induces Apoptosis in Pancreatic Cancer Cells by Targeting IGF-1R.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 10;8(5):e61015. doi: 10.1371/journal.pone.0061015. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061015](http://1371/journal.pone.0061015)

**AUTORES / AUTHORS:** - Farhana L; Dawson MI; Murshed F; Das JK; Rishi AK; Fontana JA

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Wayne State University, Detroit, Michigan, United States of America ; John D. Dingell VA Medical

Center, Detroit, Michigan, United States of America ; Wayne State University, Detroit, Michigan, United States of America ; Karmanos Cancer Institute, Detroit, Michigan, United States of America.

**RESUMEN / SUMMARY:** - MicroRNAs have been implicated in many critical cellular processes including apoptosis. We have previously found that apoptosis in pancreatic cancer cells was induced by adamantyl retinoid-related (ARR) molecule 3-CI-AHPC. Here we report that 3-CI-AHPC-dependent apoptosis involves regulating a number of microRNAs including miR-150\* and miR-630. 3-CI-AHPC stimulated miR-150\* expression and caused decreased expression of c-Myb and IGF-1R in the pancreatic cancer cells. 3-CI-AHPC-mediated reduction of c-Myb resulted in diminished binding of c-Myb with IGF-1R and Bcl-2 promoters, thereby causing repression of their transcription and protein expression. Over-expression of miR-150\* also resulted in diminished levels of c-Myb and Bcl-2 proteins. Furthermore, the addition of the miRNA inhibitor 2'-O-methylated miR-150 blocked 3-CI-AHPC-mediated increase in miR-150\* levels and abrogated loss of c-Myb protein. Knockdown of c-Myb in PANC-1 cells resulted in enhanced apoptosis both in the presence or absence of 3-CI-AHPC confirming the anti-apoptotic property of c-Myb. Overexpression of miR-630 also induced apoptosis in the pancreatic cancer cells and inhibited target protein IGF-1R mRNA and protein expression. Together these results implicate key roles for miR-150\* and miR-630 and their targeting of IGF-1R to promote apoptosis in pancreatic cancer cells.

[1055]

**TÍTULO / TITLE:** - Gambogic acid induces mitochondria-dependent apoptosis by modulation of Bcl-2 and Bax in mantle cell lymphoma JeKo-1 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin J Cancer Res. 2013 Apr;25(2):183-91. doi: 10.3978/j.issn.1000-9604.2013.02.06.

●●Enlace al texto completo (gratis o de pago) [3978/j.issn.1000-9604.2013.02.06](#)

**AUTORES / AUTHORS:** - Xu J; Zhou M; Ouyang J; Wang J; Zhang Q; Xu Y; Xu Y; Zhang Q; Xu X; Zeng H

**INSTITUCIÓN / INSTITUTION:** - Nanjing Drum Tower Hospital Clinical College of Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210038, PR China;

**RESUMEN / SUMMARY:** - OBJECTIVE: To study the mechanisms in gambogic acid (GA) -induced JeKo-1 human Mantle Cell Lymphoma cell apoptosis in vitro. METHODS: The proliferation of GA-treated JeKo-1 cells was measured by CCK-8 assay and Ki-67 immunocytochemical detection. Apoptosis, cell cycle and mitochondrial membrane potential were measured by flow cytometric analysis. Caspase-3, -8 and -9 were detected by colorimetric assay. Bcl-2 and Bax were analyzed by Western blotting. RESULTS: GA inhibited cell growth in a time- and dose- dependent manner. GA induces apoptosis in JeKo-1 cells but

not in normal bone marrow cells, which was involved in reducing the membrane potential of mitochondria, activating caspases-3, -8 and -9 and decreasing the ratio of Bcl-2 and Bax without cell cycle arresting. CONCLUSIONS: GA induced apoptosis in human MCL JeKo-1 cells by regulating Bcl-2/Bax and activating caspase-3, -8 and -9 via mitochondrial pathway without affecting cell cycle.

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[1056]

**TÍTULO / TITLE:** - Exploring the Relationship between the Inhibition Selectivity and the Apoptosis of Roscovitine-Treated Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Anal Methods Chem. 2013;2013:389390. doi: 10.1155/2013/389390. Epub 2013 Apr 4.

●●Enlace al texto completo (gratis o de pago) [1155/2013/389390](#)

**AUTORES / AUTHORS:** - Cui C; Wang Y; Wang Y; Zhao M; Peng S

**INSTITUCIÓN / INSTITUTION:** - College of Pharmaceutical Sciences, Capital Medical University, Beijing 100069, China.

**RESUMEN / SUMMARY:** - THE ANTITUMOR ACTIVITY OF ROSCOVITINE WAS TESTED IN FOUR CERVICAL CARCINOMA CELLS: C33A, HCE-1, HeLa, and SiHa. The effects of roscovitine on ATP Lite assay, cell cycle, and apoptosis were assessed. The Sub-G1 DNA content occurred great increasing, and this indicates that apoptosis was induced quickly in HeLa cells, but slowly in the other cells. The morphological observation results showed that roscovitine induced apoptosis and cell death in the cervical carcinoma cells. Results revealed that roscovitine exhibited selective cytotoxicity towards 4 cervical carcinoma cells, and the cells showed different morphologic and apoptotic changes at the same concentration. It was estimated that cervical carcinoma cells responded differently to roscovitine because of differences in apoptotic and genetic background in different cervical carcinoma cells. This study suggested that roscovitine had the potential to be a chemotherapeutic agent against cervical carcinoma.

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[1057]

**TÍTULO / TITLE:** - Casticin induces caspase-mediated apoptosis via activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Trop Med. 2013 May 13;6(5):372-8. doi: 10.1016/S1995-7645(13)60041-3.

●●Enlace al texto completo (gratis o de pago) [1016/S1995-7645\(13\)60041-3](#)

**AUTORES / AUTHORS:** - Zhou Y; Peng Y; Mao QQ; Li X; Chen MW; Su J; Tian L; Mao NQ; Long LZ; Quan MF; Liu F; Zhou SF; Zhao YX

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology of Medical College, Hunan Normal University, Changsha, Hunan 410013, China.

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**RESUMEN / SUMMARY:** - OBJECTIVE: To assess if casticin induces caspase-mediated apoptosis via activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells. METHODS: Human non-small-cell lung carcinoma cell lines H460, A549 and H157 were cultured in vitro. The cytotoxic activities were determined using MTT assay. The apoptotic cells death was examined by flow cytometry using PI staining and DNA agarose gel electrophoresis. The activities of caspase-3, -8 and -9 were measured via ELISA. Cellular fractionation was determined by flow cytometry to assess release of cytochrome c and the mitochondrial transmembrane potential. Bcl-2/Bcl-XL/XIAP/Bid/DR5 and DR4 proteins were analyzed using western blot. RESULTS: The concentrations required for a 50% decrease in cell growth (IC(50)) ranged from 1.8 to 3.2  $\mu$ M. Casticin induced rapid apoptosis and triggered a series of effects associated with apoptosis by way of mitochondrial pathway, including the depolarization of the mitochondrial membrane, release of cytochrome c from mitochondria, activation of procaspase-9 and -3, and increase of DNA fragments. Moreover, the pan caspase inhibitor zVAD-FMK and the caspase-3 inhibitor zDEVD-FMK suppressed casticin-induced apoptosis. In addition, casticin induced XIAP and Bcl-XL down-regulation, Bax upregulation and Bid clearance. In H157 cell line, casticin increased expression of DR5 at protein levels but not affect the expression of DR4. The pretreatment with DR5/Fc chimera protein effectively attenuated casticin-induced apoptosis in H157 cells. No correlation was found between cell sensitivity to casticin and that to p53 status, suggesting that casticin induce a p53-independent apoptosis. CONCLUSIONS: Our results demonstrate that casticin induces caspase-mediated apoptosis via activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells.

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[1058]

**TÍTULO / TITLE:** - Comparative proteomics analysis of sodium selenite-induced apoptosis in human prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Metallomics. 2013 May 1;5(5):541-50. doi: 10.1039/c3mt00002h. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1039/c3mt00002h](#)

**AUTORES / AUTHORS:** - Chen P; Wang L; Li N; Liu Q; Ni J

**INSTITUCIÓN / INSTITUTION:** - College of Life Sciences, Shenzhen Key Laboratory of Microbial Genetic Engineering, Shenzhen University, Shenzhen, Guangdong, P.R. China. [jzni@szu.edu.cn](mailto:jzni@szu.edu.cn).

**RESUMEN / SUMMARY:** - Selenium is an important trace mineral necessary for human health. Clinical trials have shown potential inhibitory effects of selenium in advanced or aggressive prostate cancer. However, its mechanism of action remains unclear. This study investigated the mechanism of action of sodium selenite in human prostate cancer PC-3 cells using proteomics. CCK-8 assays were used to detect cell viability and the inhibitory rate. Cell apoptosis was

detected by annexin V-FITC and propidium iodide double staining using flow cytometry. Selenite inhibited the growth of PC-3 cells causing them to display morphological changes typical of apoptosis. The rate of cell apoptosis also increased. Proteomics identified a variety of differentially expressed proteins in PC-3 cells exposed to selenite. Eighteen protein spots were identified by MALDI-TOF mass spectrometry. These proteins were separated into those involved in redox balance, protein degradation and cellular energy metabolism. Three differently expressed proteins (SOD1, Stathmin and Erp29) were chosen for Western blot verification, together with several apoptosis-related proteins. Western blot analyses showed that selenite-induced apoptosis was accompanied by activation of caspase-8 and specific proteolytic cleavage of PARP. This led to an increase in the pro-apoptotic protein Bax, and to a decrease in the anti-apoptotic protein Bcl-2 and in hypoxia inducible factor-1alpha. Increased ROS generation and decreased mitochondrial membrane potential were consistent with reduced expression of antioxidative proteins identified by comparative proteomics. We therefore propose that sodium selenite induces the apoptosis of PC-3 cells mainly through the mitochondrial pathway, but also via ER stress and HIF-1alpha mediated pathways.

[1059]

**TÍTULO / TITLE:** - Development of a miR-26 companion diagnostic test for adjuvant interferon-alpha therapy in hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Biol Sci. 2013;9(3):303-12. doi: 10.7150/ijbs.6214. Epub 2013 Mar 16.

●●Enlace al texto completo (gratis o de pago) [7150/ijbs.6214](#)

**AUTORES / AUTHORS:** - Ji J; Yu L; Yu Z; Forgues M; Uenishi T; Kubo S; Wakasa K; Zhou J; Fan J; Tang ZY; Fu S; Zhu H; Jin JG; Sun HC; Wang XW

**INSTITUCIÓN / INSTITUTION:** - Liver Carcinogenesis Section, Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA. [jjun@mail.nih.gov](mailto:jjun@mail.nih.gov)

**RESUMEN / SUMMARY:** - BACKGROUND & AIMS: Adjuvant therapies for hepatocellular carcinoma (HCC) such as interferon-alpha are effective only in a subset of patients. Previously we found that HCC patients with low level of miR-26 have survival benefits from interferon-alpha. The purpose of this study is to develop a standardized miR-26 diagnostic test (referred as MIR26-DX) to assist identification of candidate HCC patients for adjuvant interferon-alpha therapy. METHODS: We developed a multiplex reverse-transcription quantitative polymerase-chain-reaction assay to determine the levels of two HCC-related miR-26 transcripts along with six small RNA reference transcripts. We evaluated archived paraffin-embedded tissues from three cohorts of HCC patients (n=248) who underwent radical resection at three different clinical centers. Fifty-two percent of them underwent adjuvant interferon-alpha therapy. We used Cox-Mantel log-rank test to evaluate patient survival. RESULTS: We

found that the multiplexing assay was stable and reproducible regardless of differences in sample preparations and operators. We developed a matrix template and a scoring algorithm based on a training cohort (n=129) to assign HCC patients, and then applied the template in two test cohorts (n=119). The proportions of HCC patients assigned as low miR-26 by this algorithm were 68, 4, and 63 percent in the training cohort and two test cohorts, respectively. Consistently, HCC with low miR-26 had a favorable response to interferon-alpha with improved median overall survival ( $\geq 3$  year). CONCLUSIONS: MIR26-DX is a simple and reliable companion diagnostic test to select HCC patients for adjuvant interferon-alpha therapy.

[1060]

**TÍTULO / TITLE:** - Gene expression study related with the intrinsic pathway of apoptosis in bladder cancer by real-time PCR technique.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Res. 2013 Apr 2;12(2):878-86. doi: 10.4238/2013.April.2.4.

●●Enlace al texto completo (gratis o de pago) [4238/2013.April.2.4](#)

**AUTORES / AUTHORS:** - Barione DF; Lizarte FS; Novais PC; de Carvalho CA; Valeri FC; Peria FM; de Oliveira HF; Zanette DL; Silva WA Jr; Cologna AJ; Reis RB; Tucci S Jr; Martins AC; Tirapelli DP; Tirapelli LF

**INSTITUCIÓN / INSTITUTION:** - Departamento de Cirurgia e Anatomia, Faculdade de Medicina de Ribeirao Preto, Universidade de Sao Paulo, Ribeirao Preto, SP, Brasil.

**RESUMEN / SUMMARY:** - We examined the expression of anti-apoptotic genes (XIAP and Bcl-2) and apoptotic genes (cytochrome c, caspase-9, Apaf-1) in tissue samples of patients with superficial bladder cancer. Thirty-two bladder cancer tissue samples (8 papillary urothelial neoplasm of low malignant potential, 10 low-grade, and 14 high-grade) and 8 normal bladder tissue samples from necropsy were used for the study of gene expression by real-time PCR analysis. Analysis of the expression of apoptotic gene constituents of an apoptosome demonstrated an increase in Apaf-1 expression in the three tumor grades when compared with the control ( $P < 0.01$ ,  $P < 0.05$ , and  $P < 0.01$ ), low expression of caspase-9 in all groups ( $P < 0.05$ ), and an increase in cytochrome c expression in all tumor grades in relation to the control, although without statistically significant difference. The expression of anti-apoptotic genes revealed an increase in XIAP expression in all tumor grades in relation to the control, although without statistically significant difference, and low expression of Bcl-2 in all tumor grades and the control ( $P < 0.05$ ). The results proved that there is low evidence of apoptotic activity by the intrinsic pathway, demonstrated by the low expression of caspase-9 and considerable increase in XIAP expression, which may render these genes potential therapeutic targets in bladder cancer treatment.

[1061]

**TÍTULO / TITLE:** - An Aptamer-siRNA Chimera Silences the Eukaryotic Elongation Factor 2 Gene and Induces Apoptosis in Cancers Expressing alphavbeta3 Integrin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nucleic Acid Ther. 2013 Jun;23(3):203-12. doi: 10.1089/nat.2012.0408. Epub 2013 Apr 1.

●●Enlace al texto completo (gratis o de pago) [1089/nat.2012.0408](#)

**AUTORES / AUTHORS:** - Hussain AF; Tur MK; Barth S

**INSTITUCIÓN / INSTITUTION:** - 1 Department of Experimental Medicine and Immunotherapy, Institute of Applied Medical Engineering, Helmholtz-Institute for Biomedical Engineering, Aachen, Germany.

**RESUMEN / SUMMARY:** - Small interfering RNAs (siRNAs) silence gene expression by triggering the sequence-specific degradation of mRNAs, but the targeted delivery of such reagents remains challenging and a significant obstacle to therapeutic applications. One promising approach is the use of RNA aptamers that bind tumor-associated antigens to achieve the delivery of siRNAs to tumor cells displaying specific antigens. Wholly RNA-based constructs are advantageous because they are inexpensive to synthesize and their immunogenicity is low. We therefore joined an aptamer-recognizing alpha V and integrin beta 3 (alphavbeta3) integrin to a siRNA that targets eukaryotic elongation factor 2 and achieved for the first time the targeted delivery of a siRNA to tumor cells expressing alphavbeta3 integrin, causing the inhibition of cell proliferation and the induction of apoptosis specifically in tumor cells. The impact of our results on the development of therapeutic aptamer-siRNA constructs is discussed.

[1062]

**TÍTULO / TITLE:** - Artificial antigen-presenting cells plus IL-15 and IL-21 efficiently induce melanoma-specific cytotoxic CD8(+) CD28(+) T lymphocyte responses.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Trop Med. 2013 Jun;6(6):467-72. doi: 10.1016/S1995-7645(13)60076-0.

●●Enlace al texto completo (gratis o de pago) [1016/S1995-7645\(13\)60076-0](#)

**AUTORES / AUTHORS:** - Yu X; He J; Mongkhoun S; Peng Y; Xie Y; Su J; Zhou SF; Xie XX; Luo GR; Fang Y; Li X; Li X; Zhou N; Zhao YX; Lu XL

**INSTITUCIÓN / INSTITUTION:** - Biological Targeting Diagnosis and Therapy Research Center, Guangxi Medical University, Nanning, Guangxi 530021, P. R. China.

**RESUMEN / SUMMARY:** - OBJECTIVE: To develop a novel artificial antigen-presenting system for efficiently inducing melanoma-specific CD8(+) CD28(+) cytotoxic T lymphocyte (CTL) responses. METHODS: Cell-sized Dynabeads® M-450 Epoxy beads coated with H-2K(b): Ig-TRP2180-188 and anti-CD28

antibody were used as artificial antigen-presenting cells (aAPCs) to induce melanoma-specific CD8(+)CD28(+) CTL responses with the help of IL-21 and IL-15. Dimer staining, proliferation, ELISPOT, and cytotoxicity experiments were conducted to evaluate the frequency and activity of induced CTLs. RESULTS: Dimer staining demonstrated that the new artificial antigen-presenting system efficiently induced melanoma TRP2-specific CD8(+)CD28(+)CTLs. Proliferation and ELISPOT assays indicated that the induced CTLs rapidly proliferate and produce increased IFN- gamma under the stimulation of H-2K(b): Ig-TRP2-aAPCs, IL-15, and IL-21. In addition, cytotoxicity experiments showed that induced CTLs have specific killing activity of target cells. CONCLUSIONS: The new artificial antigen-presenting system including aAPCs plus IL-21 and IL-15 can induce a large number of antigen-specific CD8(+) CD28(+) CTLs against the melanoma. Our study provides evidence for a novel adoptive immunotherapy against tumors.

[1063]

**TÍTULO / TITLE:** - Processed Panax ginseng, Sun Ginseng, Decreases Oxidative Damage Induced by tert-butyl Hydroperoxide via Regulation of Antioxidant Enzyme and Anti-apoptotic Molecules in HepG2 Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Ginseng Res. 2012 Jul;36(3):248-55. doi: 10.5142/jgr.2012.36.3.248.

●●Enlace al texto completo (gratis o de pago) [5142/jgr.2012.36.3.248](#)

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**INSTITUCIÓN / INSTITUTION:** - Lab of Cell Differentiation Research, College of Oriental Medicine, Gachon University, Seongnam 461-701, Korea.

**RESUMEN / SUMMARY:** - Potential antioxidant effect of processed ginseng (sun ginseng, SG) on oxidative stress generated by tert-butyl hydroperoxide (t-BHP) was investigated in HepG2 cells. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and lactate dehydrogenase (LDH) leakage test demonstrated that SG dose-dependently prevents a loss of cell viability against t-BHP-induced oxidative stress. Also, SG treatment dose-dependently relieved the increment of activities of hepatic enzymes, such as aspartate aminotransferase and alanine aminotransferase, and lipid peroxidation mediated by t-BHP treatment in HepG2 cells. SG increased the gene expression of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. However, high dose of SG treatment caused decrease in mRNA level of glutathione peroxidase as compared to low dosage of SG-treated cells. The gene expression of glutathione reductase was found to be slightly increased by SG treatment. In addition, SG extract attributed its hepatoprotective effect by inducing the mRNA level of bcl-2 and bcl-xL but reducing that of bax. But, the gene expression of bad showed no significant change in SG-treated HepG2 cells. These findings suggest that SG has hepatoprotective effect by showing reduction of LDH release, activities of hepatic enzymes and lipid

peroxidation and regulating the gene expression of antioxidant enzymes and apoptosis-related molecules against oxidative stress caused by t-BHP in HepG2 cells.

[1064]

**TÍTULO / TITLE:** - Activation of Wnt signaling inhibits the pro-apoptotic role of Notch in gastric cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jun;7(6):1751-6. doi: 10.3892/mmr.2013.1412. Epub 2013 Apr 3.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1412](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, China Medical University, Shenyang, Liaoning 110001, P.R. China.

**RESUMEN / SUMMARY:** - Notch and Wnt signaling play critical roles in the regulation of development and diseases. Several studies have previously reported that Notch may be a therapeutic target in the treatment of various types of human cancer. In this study, we report that activation of Notch1 inhibits the proliferation of BGC-823 gastric cancer cells. However, the activation of the Wnt/betacatenin signaling pathway promotes the growth of BGC-823 cells. Furthermore, the combinational activation of the two signaling pathways promotes the proliferation of BGC-823 cells. These data suggest that the activation of Wnt signaling overcomes the pro-apoptotic role of Notch in BGC-823 gastric cancer cells.

[1065]

**TÍTULO / TITLE:** - Evaluation of Serum Calcium as a Predictor of Biochemical Recurrence following Salvage Radiation Therapy for Prostate Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - ISRN Oncol. 2013 Mar 31;2013:239241. doi: 10.1155/2013/239241. Print 2013.

●●Enlace al texto completo (gratis o de pago) [1155/2013/239241](#)

**AUTORES / AUTHORS:** - Peterson JL; Buskirk SJ; Heckman MG; Parker AS; Diehl NN; Tzou KS; Paryani NN; Ko SJ; Daugherty LC; Vallow LA; Pisansky TM

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Mayo Clinic Florida, Jacksonville, FL 32224, USA.

**RESUMEN / SUMMARY:** - Background. Previous reports have shown a positive association between serum calcium level and prostate cancer mortality. However, there is no data regarding whether higher serum calcium levels are associated with increased risk of biochemical recurrence (BCR) following salvage radiation therapy (SRT) for prostate cancer. Herein, we evaluate the association between pretreatment serum calcium levels and BCR in a cohort of men who underwent SRT. Methods. We evaluated 165 patients who underwent SRT at our institution. Median dose was 65.0 Gy (range: 54.0-72.4 Gy). We

considered serum calcium as both a continuous variable and a 3-level categorical variable (low [ $\leq 9.0$  mg/dL], moderate [ $> 9.0$  mg/dL and  $\leq 9.35$  mg/dL], and high [ $> 9.35$  mg/dL]) based on sample tertiles. Results. We observed no evidence of a linear association between serum calcium and BCR (relative risk (RR): 0.96,  $P = 0.76$ ). Compared to men with low calcium, there was no significantly increased risk of BCR for men with moderate (RR: 0.94,  $P = 0.79$ ) or high (RR: 1.08,  $P = 0.76$ ) serum calcium levels. Adjustment for clinical, pathological, and SRT characteristics in multivariable analyses did not alter these findings. Conclusion. Our results provide evidence that pretreatment serum calcium is unlikely to be a useful tool in predicting BCR risk following SRT.

[1066]

**TÍTULO / TITLE:** - Cisplatin-induced caspase activation mediates PTEN cleavage in ovarian cancer cells: a potential mechanism of chemoresistance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 10;13:233. doi: 10.1186/1471-2407-13-233.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-233](#)

**AUTORES / AUTHORS:** - Singh M; Chaudhry P; Fabi F; Asselin E

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Biology, Research group in Molecular Oncology and Endocrinology, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada. [eric.asselin@uqtr.ca](mailto:eric.asselin@uqtr.ca).

**RESUMEN / SUMMARY:** - BACKGROUND: The phosphatase and tensin homolog deleted on chromosome 10 (PTEN) tumor suppressor protein is a central negative regulator of the PI3K/AKT signaling cascade and suppresses cell survival as well as cell proliferation. PTEN is found to be either inactivated or mutated in various human malignancies. In the present study, we have investigated the regulation of PTEN during cisplatin induced apoptosis in A2780, A270-CP (cisplatin resistant), OVCAR-3 and SKOV3 ovarian cancer cell lines. METHODS: Cells were treated with 10  $\mu$ M of cisplatin for 24h. Transcript and protein levels were analysed by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) and western blotting, respectively. Immunofluorescence microscopy was used to assess the intracellular localization of PTEN. Proteasome inhibitor and various caspase inhibitors were used to find the mechanism of PTEN degradation. RESULTS: PTEN protein levels were found to be decreased significantly in A2780 cells; however, there was no change in PTEN protein levels in A2780-CP, OVCAR-3 and SKOV3 cells with cisplatin treatment. The decrease in PTEN protein was accompanied with an increase in the levels of AKT phosphorylation (pAKT) in A2780 cells and a decrease of BCL-2. Cisplatin treatment induced the activation/cleavage of caspase-3, -6, -7, -8, -9 in all cell lines tested in this study except the resistant variant A2780-CP cells. In A2780 cells, restoration of PTEN levels was achieved upon pre-treatment with Z-DEVD-FMK (broad range

caspases inhibitor) and not with MG132 (proteasome inhibitor) and by overexpression of BCL-2, suggesting that caspases and BCL-2 are involved in the decrease of PTEN protein levels in A2780 cells. CONCLUSION: The decrease in pro-apoptotic PTEN protein levels and increase in survival factor pAKT in A2780 ovarian cancer cells suggest that cisplatin treatment could further exacerbate drug resistance in A2780 ovarian cancer cells.

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[1067]

**TÍTULO / TITLE:** - Fatal recrudescence of malignant hyperthermia in an infant with moebius syndrome.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Rev Bras Anesthesiol. 2013 May-Jun;63(3):296-300. doi: 10.1016/S0034-7094(13)70234-4.

●●Enlace al texto completo (gratis o de pago) [1016/S0034-7094\(13\)70234-4](#)

**AUTORES / AUTHORS:** - Fernandes CR; Pinto Filho WA; Cezar LC; Alves Gomes JM; Florencio da Cunha GK

**INSTITUCIÓN / INSTITUTION:** - TSA; Co-responsible for CET/MEC/SBA, Hospital Universitario Walter Cantidio, UFC; Anesthesiologist, Hospital Infantil Albert Sabin, Secretary of Health of Ceara, Fortaleza, Ceara, Brazil. Electronic address: [claugifer@gmail.com](mailto:claugifer@gmail.com).

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVES: Malignant hyperthermia (MH) is a pharmacogenetic skeletal muscle disorder characterized by a hypermetabolic state after anesthesia with succinylcholine and/ or volatile anesthetics. Various neuromuscular syndromes are associated with susceptibility; however, Moebius syndrome has not been reported. Dantrolene is the drug of choice for treatment. Recurrence may occur in up to 20% of cases after the initial event treatment. CASE REPORT: Male infant, first twin, 7 months old, weighing 6.5kg and presenting with Moebius syndrome was admitted for clubfoot repair. The patient had MH after exposure to sevoflurane and succinylcholine, which was readily reversed with dantrolene maintained for 24 hours. Ten hours after dantrolene discontinuation, there was recrudescence of MH that did not respond satisfactorily to treatment, and the patient died. DISCUSSION: Musculoskeletal disorders in children are associated with increased risk of developing MH, although Moebius syndrome has not yet been reported. Dantrolene is the drug of choice for treating this syndrome; prophylaxis is indicated during the first 24-48 hours of the episode onset. The main risk factors for recurrence are muscular type, long latency after anesthetic exposure, and increased temperature. The child had only one risk factor. This case leads us to reflect on how we must be attentive to children with musculoskeletal disease and maintain treatment for 48 hours.

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[1068]

**TÍTULO / TITLE:** - Interest in Determining the CD34+ CD38- Phenotype in the Diagnosis and Prognosis of Acute Leukemia in Abidjan - Cote d'Ivoire.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mediterr J Hematol Infect Dis. 2013 Apr 10;5(1):e2013023. doi: 10.4084/MJHID.2013.023. Print 2013.

●●Enlace al texto completo (gratis o de pago) [4084/MJHID.2013.023](#)

**AUTORES / AUTHORS:** - Sawadogo D; Tolo A; Kassi H; Sangare M; Inwoley A

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology. Faculty of Pharmacy. University Felix Houphouet Boigny. Cocody. Abidjan. Unit of Hematology. Central Laboratory. Teaching Hospital of Yopougon. Abidjan.

**RESUMEN / SUMMARY:** - BACKGROUND: In Cote d'Ivoire, acute leukemias account for 12.5% of hematological malignancies. Acute leukemias are due to an anomaly of the stem cell characterized among other things by the expression of CD34(+) CD38(-) surface markers. This CD34(+) CD38(-) phenotype as well as other factors such as tumor syndrome, high leukocytosis and blasts are considered as important factors of poor prognosis. We therefore proposed to investigate the prognostic value of the expression of CD34(+) CD38(-) markers in acute leukemias in Abidjan. METHODS: We selected 23 patients aged 33 years on whom we performed Complete Blood Count, bone marrow aspiration and immunophenotyping. To search for myeloperoxidase, smears of blood or bone marrow were stained with benzidine and revealed by the use of Hydrogen peroxide. Acute leukemias were then identified and distributed using the score proposed by the European Group for the Immunological characterization of Leukemias. The definitive diagnosis was made by combining morphological characters that serve as the basis for the French-American-British classification as well as cytochemical and immunophenotypic characters. RESULTS: According to the cytological and immunophenotypic classifications, the acute lymphoid leukemia 2 and B IV predominated. 52.2% (12/33) of patients were CD34(+) CD38(-). This phenotype was found in almost all cytological immunophenotypic types. The medullary invasion by blasts (reflection of the tumor mass) of the total sample of CD34(+), CD34(+) CD38(-) patients and those not expressing CD34(+) was respectively 79.4%, 81.25%, 83.3% and 74.8%. CONCLUSION: There was therefore no correlation between medullary blasts and the expression of CD34(+) CD38(-). To the factors we selected it would have been necessary to associate the study of cytogenetic and molecular anomalies to better understand the role of CD34(+) CD38(-) phenotype, concerning prognosis.

[1069]

**TÍTULO / TITLE:** - Colon cancer cells adopt an invasive phenotype without mesenchymal transition in 3-D but not 2-D culture upon combined stimulation with EGF and crypt growth factors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 2;13:221. doi: 10.1186/1471-2407-13-221.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-221](https://doi.org/10.1186/1471-2407-13-221)

**AUTORES / AUTHORS:** - Ludwig K; Tse ES; Wang JY

**INSTITUCIÓN / INSTITUTION:** - Moores UCSD Cancer Center, 3855 Health Sciences Drive, La Jolla, CA, 92093-0820, USA. [jywang@ucsd.edu](mailto:jywang@ucsd.edu).

**RESUMEN / SUMMARY:** - **BACKGROUND:** The intestinal crypt homeostasis is maintained by a combination of growth factors including Wnt, R-Spondin1, Noggin and the epidermal growth factor (EGF). In human colorectal cancer, the Wnt pathway is constitutively activated through genetic and epigenetic alterations in as many as 11 genes encoding components of this crypt stem-cell maintenance mechanism. Although the proliferation of colon cancer cells does not require Wnt, it is possible that colon cancer cells can still respond to the crypt growth factors in the colonic microenvironment. A number of studies have shown that epithelial cells behave differently in 3-D versus 2-D cultures. Because the 3-D conditions more closely mimic the in vivo environment, we examined the effects of Wnt and other crypt growth factors on colon cancer cell growth in 3-D culture. **METHODS:** Colon cancer cells were grown in 3-D matrigel supplemented with different combinations of crypt growth factors and colonies were examined for morphology and pathways. **RESULTS:** When colon cancer cells were cultured in 3-D with EGF, they grew as round spheroid colonies. However, colon cancer cells also grew as flat, disc-like colonies when cultured with EGF plus Wnt, R-Spondin1 and Noggin. Disc colonies were found to have comparable levels of E-cadherin as the spheroid colonies, but showed decreased E-cadherin at the cell-matrix contact sites. Disc colonies also elaborated F-actin rich protrusions (FRP) at the cell-matrix edge, reminiscent of an invasive phenotype but without the expression of vimentin. These E-cadherin and F-actin alterations were not induced by the four growth factors in 2-D culture. Formation of the disc colonies was inhibited by the knockdown of beta-catenin and by protein kinase inhibitors such as gefitinib, imatinib and MK-2206. Furthermore, withdrawal of the crypt growth factors was able to revert the disc colonies to spheroid growth, showing that the invasive phenotype was reversible dependent on the availability of growth factors. **CONCLUSIONS:** These findings show that colon cancer cells remain responsive to the growth factors in the crypt microenvironment and can be induced to undergo morphological transformation in the more physiologically relevant 3-D culture.

[1070]

**TÍTULO / TITLE:** - Combined treatment with verrucarin A and tumor necrosis factor-alpha sensitizes apoptosis by overexpression of nuclear factor-kappaB-mediated Fas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Environ Toxicol Pharmacol. 2013 Apr 25;36(2):303-310. doi: 10.1016/j.etap.2013.04.008.

●●Enlace al texto completo (gratis o de pago) [1016/j.etap.2013.04.008](http://1016/j.etap.2013.04.008)

**AUTORES / AUTHORS:** - Jayasooriya RG; Moon DO; Park SR; Choi YH; Asami Y; Kim MO; Jang JH; Kim BY; Ahn JS; Kim GY

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Immunobiology, Department of Marine Life Sciences, Jeju National University, Ara-1 dong, Jeju 690-756, Republic of Korea.

**RESUMEN / SUMMARY:** - Verrucarín A (VA) es un miembro de la familia de macrocíclicos trichothecenos, que exhiben actividad anti-cáncer y moduladora inmune. Sin embargo, VA no ha sido demostrada involucrada en la sensibilización de la apoptosis mediada por el factor de necrosis tumoral- $\alpha$  (TNF- $\alpha$ ). En el presente estudio, encontramos que VA induce apoptosis en células de cáncer de mama humano MDA-MB-231 y MCF-7. En particular, la activación de caspasas-3 y caspasa-8 así como la liberación de citocromo c fueron significativamente mejoradas en respuesta al tratamiento combinado con VA y TNF- $\alpha$  (VA/TNF- $\alpha$ ) y el inhibidor pan-caspasa z-VAD-fmk completamente revertió la apoptosis, sugiriendo que las caspasas son las moléculas efectoras principales en la apoptosis inducida por VA/TNF- $\alpha$  a través de la vía intrínseca y extrínseca. Además, confirmamos que la expresión mejorada de Fas juega un papel crítico, porque el anticuerpo bloqueador de Fas parcialmente inhibió la apoptosis inducida por VA/TNF- $\alpha$ . VA también aumentó la actividad de unión específica al ADN del factor nuclear  $\kappa$ B (NF- $\kappa$ B) a través de la translocación nuclear de p50 y p65. Además, el tratamiento previo con el inhibidor de NF- $\kappa$ B MG132 bloqueó la apoptosis inducida por VA/TNF- $\alpha$  por supresión de la expresión de Fas dependiente de NF- $\kappa$ B. Estos resultados indican que VA mejora la apoptosis inducida por TNF- $\alpha$  a través de la sobreexpresión dependiente de NF- $\kappa$ B de Fas.

[1071]

**TÍTULO / TITLE:** - Resveratrol promotes proteasome-dependent degradation of Nanog via p53 activation and induces differentiation of glioma stem cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Stem Cell Res. 2013 Jul;11(1):601-10. doi: 10.1016/j.scr.2013.04.004. Epub 2013 Apr 11.

●●Enlace al texto completo (gratis o de pago) [1016/j.scr.2013.04.004](http://1016/j.scr.2013.04.004)

**AUTORES / AUTHORS:** - Sato A; Okada M; Shibuya K; Watanabe E; Seino S; Suzuki K; Narita Y; Shibui S; Kayama T; Kitanaka C

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**RESUMEN / SUMMARY:** - Glioblastoma is the most common and aggressive primary brain tumor. Glioma stem cells (GSCs) are relatively resistant to chemo-radiotherapy and are responsible for tumor progression and the recurrence of glioblastomas after conventional therapy. Thus, the control of the GSC population is considered key to realizing long-term survival of glioblastoma.

patients. Here, we identified that resveratrol significantly reduced the self-renewal and tumor-initiating capacity of patient-derived GSCs. Furthermore, resveratrol promoted Nanog suppression via proteasomal degradation, which was inhibited by MG132, a proteasome inhibitor. p53 activation is an important factor in Nanog suppression and treatment with resveratrol was also found to activate the p53/p21 pathway. Importantly, inhibition of Nanog by siRNA provoked inhibitory effects on both the self-renewal and tumor-forming capacity of GSCs. Our findings indicate that Nanog is an essential factor for the retention of stemness and may contribute to the resveratrol-induced differentiation of GSCs. Our results also suggest that targeting GSCs via the p53-Nanog axis, with resveratrol for instance, could be a therapeutic strategy against glioblastoma.

[1072]

**TÍTULO / TITLE:** - Repeated favorable responses to epidermal growth factor receptor-tyrosine kinase inhibitors in a case of advanced lung adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tuberc Respir Dis (Seoul). 2013 Mar;74(3):129-33. doi: 10.4046/trd.2013.74.3.129. Epub 2013 Mar 29.

●●Enlace al texto completo (gratis o de pago) [4046/trd.2013.74.3.129](#)

**AUTORES / AUTHORS:** - Kim EY; Kim YH; Ban HJ; Oh IJ; Kwon YS; Kim KS; Kim YI; Lim SC; Kim YC

**INSTITUCIÓN / INSTITUTION:** - Lung and Esophageal Cancer Clinic, Chonnam National University Hwasun Hospital, Hwasun, Korea. ; Department of Internal Medicine, Chonnam National University Medical School, Hwasun, Korea.

**RESUMEN / SUMMARY:** - The presence of epidermal growth factor receptor (EGFR) mutation is a prognostic and predictive marker for EGFR-tyrosine kinase inhibitor (TKI) therapy. However, inevitably, relapse occurs due to the development of acquired resistance, such as T790M mutation. We report a case of repeated responses to EGFR-TKIs in a never-smoked woman with adenocarcinoma. After six cycles of gemcitabine and cisplatin, the patient was treated by gefitinib for 4 months until progression. Following the six cycles of third-line pemetrexed, gefitinib retreatment was initiated and continued with a partial response for 6 months. After progression, she was recruited for an irreversible EGFR inhibitor trial, and the time to progression was 11 months. Although EGFR direct sequencing on the initial diagnostic specimen revealed a wild-type, we performed a rebiopsy from the progressed subcarinal node at the end of the trial. The result of peptide nucleic acid clamping showed L858R/L861Q.

[1073]

**TÍTULO / TITLE:** - Long Noncoding RNA HOTAIR Is a Prognostic Marker for Esophageal Squamous Cell Carcinoma Progression and Survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 23;8(5):e63516. doi: 10.1371/journal.pone.0063516. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063516](https://doi.org/10.1371/journal.pone.0063516)

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**INSTITUCIÓN / INSTITUTION:** - Medical Research Center Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou 510120, China.

**RESUMEN / SUMMARY:** - BACKGROUND: It is currently unclear whether the expression of HOX transcript antisense RNA (HOTAIR) correlates with the progression of esophageal cancer. The aim of this study was to examine HOTAIR expression in patients with esophageal squamous cell cancer (ESCC) and explore its clinical significance. METHODS: Differences in the expression of HOTAIR were examined via in situ hybridization (ISH) and quantitative reverse transcriptase PCR (qRT-PCR). The prognostic significance was evaluated using Kaplan-Meier and Cox regression analyses. Proliferation, colony formation and migration assays were performed in ESCC cell lines to determine the function of HOTAIR in the progression of ESCC in vitro. RESULTS: A notably higher level of HOTAIR expression was found in ESCC tissues. High expression levels of HOTAIR in ESCC patients correlated positively with clinical stage, TNM classification, histological differentiation and vital status. HOTAIR expression was found to be an independent prognostic factor in ESCC patients. ESCC patients who expressed high levels of HOTAIR had substantially lower overall 5-year survival rates than HOTAIR-negative patients. In vitro assays of ESCC cell lines demonstrated that HOTAIR mediated the proliferation, colony formation and migratory capacity of ESCC cells. CONCLUSION: HOTAIR is a potential biomarker for ESCC prognosis, and the dysregulation of HOTAIR may play an important role in ESCC progression.

[1074]

**TÍTULO / TITLE:** - Cytotoxicity of tumor antigen specific human T cells is unimpaired by arginine depletion.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 23;8(5):e63521. doi: 10.1371/journal.pone.0063521. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063521](https://doi.org/10.1371/journal.pone.0063521)

**AUTORES / AUTHORS:** - Munder M; Engelhardt M; Knies D; Medenhoff S; Wabnitz G; Luckner-Minden C; Feldmeyer N; Voss RH; Kropf P; Muller I; Conradi R; Samstag Y; Theobald M; Ho AD; Goldschmidt H; Hundemer M

**INSTITUCIÓN / INSTITUTION:** - Third Department of Medicine (Hematology, Oncology, and Pneumology), University Medical Center Mainz, Mainz, Germany.

**RESUMEN / SUMMARY:** - Tumor-growth is often associated with the expansion of myeloid derived suppressor cells that lead to local or systemic arginine

depletion via the enzyme arginase. It is generally assumed that this arginine deficiency induces a global shut-down of T cell activation with ensuing tumor immune escape. While the impact of arginine depletion on polyclonal T cell proliferation and cytokine secretion is well documented, its influence on chemotaxis, cytotoxicity and antigen specific activation of human T cells has not been demonstrated so far. We show here that chemotaxis and early calcium signaling of human T cells are unimpaired in the absence of arginine. We then analyzed CD8(+) T cell activation in a tumor peptide as well as a viral peptide antigen specific system: (i) CD8(+) T cells with specificity against the MART-1aa26-35\*A27L tumor antigen expanded with in vitro generated dendritic cells, and (ii) clonal CMV pp65aa495-503 specific T cells and T cells retrovirally transduced with a CMV pp65aa495-503 specific T cell receptor were analyzed. Our data demonstrate that human CD8(+) T cell antigen specific cytotoxicity and perforin secretion are completely preserved in the absence of arginine, while antigen specific proliferation as well as IFN-gamma and granzyme B secretion are severely compromised. These novel results highlight the complexity of antigen specific T cell activation and demonstrate that human T cells can preserve important activation-induced effector functions in the context of arginine deficiency.

[1075]

**TÍTULO / TITLE:** - PIK3CA gene mutation associated with poor prognosis of lung adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Onco Targets Ther. 2013 May 7;6:497-502. doi: 10.2147/OTT.S41643. Print 2013.

●●Enlace al texto completo (gratis o de pago) [2147/OTT.S41643](#)

**AUTORES / AUTHORS:** - Zhang L; Shi L; Zhao X; Wang Y; Yue W

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular and Cellular Biology, Beijing Chest Hospital, Capital Medical University, Beijing TB and Thoracic Tumor Research Institute, Beijing, People's Republic of China.

**RESUMEN / SUMMARY:** - **PURPOSE:** PIK3CA gene mutations have been detected in many malignancies, but the frequency of different mutations and their role in the carcinogenesis of lung adenocarcinoma are still unclear. The purpose of this study was to explore the clinical pathological impact and prognostic implications of PIK3CA mutations in lung adenocarcinoma. **METHODS:** Five common PIK3CA mutations (E542K, E545K, and E545D mutation in exon 9, H1047R and H1047L mutation in exon 20) were detected by amplification refractory mutation system (ARMS) allele-specific polymerase chain reaction (PCR), in 122 patients with lung adenocarcinoma. The relationships were studied between these mutations and various clinicopathologic variables (age, lymph node status, distant metastasis, clinicopathologic stage, smoking status, and progression-free survival). **RESULTS:** In total, 25 mutations were identified, of which 24 mutations were

clustered in exon 20, and one mutation in exon 9. The most common mutations were H1047R (18 out of the 122 patients, 14.8%) in exon 20. PIK3CA-mutated tumors were more frequently found in patients with lymph node positive metastasis status ( $P < 0.05$ ). There was no significant association between PIK3CA mutations and age, distant metastasis, smoking status, or clinicopathologic stage. However, mutations were found less frequently in the early clinicopathologic stage patients (six in 50 cases, 12%) than in advanced stage (19 in 72 cases, 26.4%). Higher frequency of H1047R mutations was associated with poor prognosis, and this association reached statistical significance ( $P < 0.05$ ). CONCLUSION: Our data indicate that the PIK3CA mutations H1047R and H1047L are significant genetic alterations in lung adenocarcinoma. Among lung adenocarcinoma patients who underwent curative resection, PIK3CA mutations were associated with shorter progression-free survival. Our findings demonstrated a significant role of PIK3CA in lung adenocarcinoma.

[1076]

**TÍTULO / TITLE:** - The Metastasis-Associated Gene MTA3, a Component of the Mi-2/NuRD Transcriptional Repression Complex, Predicts Prognosis of Gastroesophageal Junction Adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 3;8(5):e62986. doi: 10.1371/journal.pone.0062986. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062986](http://1371/journal.pone.0062986)

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**INSTITUCIÓN / INSTITUTION:** - Department of Integrative Oncology, Affiliated Cancer Hospital of Shantou University Medical College, Shantou, China ; Cancer Research Center, Shantou University Medical College, Shantou, China.

**RESUMEN / SUMMARY:** - Gastroesophageal junction (GEJ) adenocarcinoma carries a poor prognosis that is largely attributable to early and frequent metastasis. The acquisition of metastatic potential in cancer involves epithelial-to-mesenchymal transition (EMT). The metastasis-associated gene MTA3, a novel component of the Mi-2/NuRD transcriptional repression complex, was identified as master regulator of EMT through inhibition of Snail to increase E-cadherin expression in breast cancer. Here, we evaluated the expression pattern of the components of MTA3 pathway and the corresponding prognostic significance in GEJ adenocarcinoma. MTA3 expression was decreased at both protein and mRNA levels in tumor tissues compared to the non-tumorous and lowed MTA3 levels were noted in tumor cell lines with stronger metastatic potential. Immunohistochemical analysis of a cohort of 128 cases exhibited that patients with lower expression of MTA3 had poorer outcomes. Combined misexpression of MTA3, Snail and E-cadherin had stronger correlation with

malignant properties. Collectively, results suggest that the MTA3-regulated EMT pathway is altered to favor EMT and, therefore, disease progression and that MTA3 expression was an independent prognostic factor in patients with GEJ adenocarcinoma.

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[1077]

**TÍTULO / TITLE:** - Indole-3-Carbinol and 3',3'-Diindolylmethane Modulate Androgen's Effect on C-C Chemokine Ligand 2 and Monocyte Attraction to Prostate Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Prev Res (Phila). 2013 Jun;6(6):519-29. doi: 10.1158/1940-6207.CAPR-12-0419. Epub 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1158/1940-6207.CAPR-12-0419](#)

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**RESUMEN / SUMMARY:** - Inflammation has a role in prostate tumorigenesis. Recruitment of inflammatory monocytes to the tumor site is mediated by C-C chemokine ligand 2 (CCL2) through binding to its receptor CCR2. We hypothesized that androgen could modulate CCL2 expression in hormone-responsive prostate cancer cells and thereby promote recruitment of monocytes. Given the inhibitory effect of broccoli-derived compounds indole-3-carbinol (I3C) and 3,3'-diindolylmethane (DIM) on androgen-dependent pathways, we also reasoned that I3C and DIM could modulate the effect of androgen on CCL2-mediated pathways. Dihydrotestosterone was found to induce a time-dependent (0-72 hours) and concentration-dependent (0-1 nmol/L) increase in CCL2 mRNA levels in androgen-responsive human prostate cancer cells (LNCaP). This increase in CCL2 mRNA corresponded with increased secretion of CCL2 protein. The effect of dihydrotestosterone was mediated through an androgen receptor (AR)-dependent pathway as small inhibitor RNA against AR negated the induction of CCL2. Although dihydrotestosterone also induced TWIST1 mRNA, an epithelial-mesenchymal transition-related factor, and purported inducer of CCL2, blocking its expression with small inhibitor RNA did not inhibit dihydrotestosterone induction of CCL2 mRNA. Moreover, conditioned media from androgen-treated cells promoted human monocyte THP-1 cell migration and this effect was blocked by antibody against CCL-2. Both I3C and DIM inhibited promotional effects of dihydrotestosterone on CCL2 and migration. These results show that androgen may regulate CCL2 and promote inflammatory microenvironment in prostate tumors and that this process can be blocked by broccoli-derived compounds. Cancer Prev Res; 6(6); 519-29. ©2013 AACR.

[1078]

**TÍTULO / TITLE:** - Germline and Somatic Mutations in Cyclin-Dependent Kinase Inhibitor Genes CDKN1A, CDKN2B, and CDKN2C in Sporadic Parathyroid Adenomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Horm Cancer. 2013 May 29.

●●Enlace al texto completo (gratis o de pago) [1007/s12672-013-0147-](#)

[9](#)

**AUTORES / AUTHORS:** - Costa-Guda J; Soong CP; Parekh VI; Agarwal SK; Arnold A

**INSTITUCIÓN / INSTITUTION:** - Center for Molecular Medicine and Division of Endocrinology and Metabolism, University of Connecticut School of Medicine, Farmington, CT, 06030, USA.

**RESUMEN / SUMMARY:** - The molecular pathogenesis of sporadic parathyroid adenomas is incompletely understood. The possible role of cyclin-dependent kinase inhibitor (CDKI) genes was raised by recognition of cyclin D1 as a parathyroid oncogene, identification of rare germline mutations in CDKI genes in patients with multiple endocrine neoplasia type 1; that in rodents, mutation in Cdkn1b caused parathyroid tumors; and subsequently through identification of rare predisposing germline sequence variants and somatic mutation of CDKN1B, encoding p27kip1, in sporadic human parathyroid adenoma. We therefore sought to determine whether mutations/variants in the other six CDKI genes CDKN1A, CDKN1C, CDKN2A, CDKN2B, CDKN2C, and CDKN2D, encoding p21, p57, p14ARF/p16, p15, p18, and p19, respectively, contribute to the development of typical parathyroid adenomas. In a series of 85 sporadic parathyroid adenomas, direct DNA sequencing identified alterations in five adenomas (6 %): Two contained distinct heterozygous changes in CDKN1A, one germline and one of undetermined germline status; one had a CDKN2B germline alteration, accompanied by loss of the normal allele in the tumor (LOH); two had variants of CDKN2C, one somatic and one germline with LOH. Abnormalities of three of the mutant proteins were readily demonstrable in vitro. Thus, germline mutations/rare variants in CDKN1A, CDKN2B, and CDKN2C likely contribute to the development of a significant subgroup of common sporadic parathyroid adenomas, and somatic mutation in CDKN2C further suggests a direct role for CDKI alteration in conferring a selective growth advantage to parathyroid cells, providing novel support for the concept that multiple CDKIs can play primary roles in human neoplasia.

[1079]

**TÍTULO / TITLE:** - TSH receptor antibodies have predictive value for breast cancer - retrospective analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Thyroid Res. 2013 May 16;6(1):8. doi: 10.1186/1756-6614-6-8.

●●Enlace al texto completo (gratis o de pago) [1186/1756-6614-6-8](#)

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**RESUMEN / SUMMARY:** - BACKGROUND: Associations between breast cancer and thyroid disorders are reported in numerous studies. Relationships between thyroperoxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb) and breast cancer have been previously demonstrated. However, no analysis has been performed concerning an association between thyrotropin (TSH) receptor antibodies (TSHRAb) and breast cancer. The aim of the study was to evaluate the prevalence of breast cancer or benign breast tumors in patients with Graves' disease and to analyze a possible relationship between Graves' disease and these two groups of breast diseases with emphasis to epidemiology and laboratory findings. PATIENTS AND METHODS: Clinical and laboratory details of 2003 women hospitalized for endocrine disorders were retrospectively analyzed, using an unpaired Student's t-test, logistic regression analysis, chi2 test of independence or the two-sided ratio comparison test. RESULTS: The coexistence of Graves' disease and breast cancer was statistically significant. We observed TSHRAb and TgAb more frequently in patients with breast cancer. We found that TSHRAb is the only variable possessing predictive value for breast cancer. CONCLUSIONS: The strong relationship between Graves' disease and breast cancer is proposed. We suggest that TSHRAb could be described as a positive determinant of breast cancer. The present data call attention to the usefulness of screening for breast cancer in long-term follow-up of patients with autoimmune thyroid disorders, especially of those with Graves' disease. Similarly, screening for autoimmune thyroid disorders should be performed in patients with nodular breast disease. Additionally, the article draws ideas for further research in order to develop targeted treatment for more successful outcome in patients with breast cancer.

[1080]

**TÍTULO / TITLE:** - Natural killer cell mediated antibody-dependent cellular cytotoxicity in tumor immunotherapy with therapeutic antibodies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Front Immunol. 2013;4:76. doi: 10.3389/fimmu.2013.00076. Epub 2013 Mar 27.

●●Enlace al texto completo (gratis o de pago) [3389/fimmu.2013.00076](#)

**AUTORES / AUTHORS:** - Seidel UJ; Schlegel P; Lang P

**INSTITUCIÓN / INSTITUTION:** - Department of General Paediatrics, Oncology/Haematology, University Children's Hospital Tubingen Tubingen, Germany.

**RESUMEN / SUMMARY:** - In the last decade several therapeutic antibodies have been Federal Drug Administration (FDA) and European Medicines Agency (EMA) approved. Although their mechanisms of action in vivo is not fully elucidated, antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer (NK) cells is presumed to be a key effector function. A substantial role of ADCC has been demonstrated in vitro and in mouse tumor models. However, a direct in vivo effect of ADCC in tumor reactivity in humans remains to be shown. Several studies revealed a predictive value of FcγRIIIa-V158F polymorphism in monoclonal antibody treatment, indicating a potential effect of ADCC on outcome for certain indications. Furthermore, the use of therapeutic antibodies after allogeneic hematopoietic stem cell transplantation is an interesting option. Studying the role of the FcγRIIIa-V158F polymorphism and the influence of Killer-cell Immunoglobulin-like Receptor (KIR) receptor ligand incompatibility on ADCC in this approach may contribute to future transplantation strategies. Despite the success of approved second-generation antibodies in the treatment of several malignancies, efforts are made to further augment ADCC in vivo by antibody engineering. Here, we review currently used therapeutic antibodies for which ADCC has been suggested as effector function.

[1081]

**TÍTULO / TITLE:** - The impact of chemotherapy-associated neutrophil/lymphocyte counts on prognosis of adjuvant chemotherapy in colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Apr 3;13:177. doi: 10.1186/1471-2407-13-177.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-177](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, Lab of Surgery, the Second Affiliated Hospital of Guangzhou Medical University, 250 Chang-gang-dong Road, Guangzhou 510260, Guangdong Province, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Leukocytes play an important role in cancer development. However, the impact of chemotherapy-associated neutropenia/lymphopenia on the prognosis of adjuvant chemotherapy is unknown. Here, we aimed to explore the impact of chemotherapy-associated neutrophil/lymphocyte counts on prognosis of adjuvant chemotherapy in colorectal cancer (CRC) and the risk factors for developing neutropenia/lymphopenia which showed impact on the prognosis of CRC receiving adjuvant chemotherapy. METHODS: From February 2003 to January 2011, 243 stage II and III CRC patients receiving adjuvant chemotherapy were enrolled in this retrospective study. The associations between neutrophil/lymphocyte counts and disease free survival (DFS)/overall survival (OS) of

CRC, and the risk factors for neutropenia/lymphopenia were investigated. RESULTS: No association of chemotherapy-associated neutrophil counts and CRC recurrence (AUC = 0.474, P = 0.534), death (AUC = 0.449, P = 0.249) was found by ROC analysis. However, the chemotherapy-associated lymphocyte counts could significantly affect CRC recurrence (AUC = 0.634, P = 0.001), or death (AUC = 0.607, P = 0.015), with a optimized cut-off of  $0.66 \times 10^9/L$  for recurrence, and  $0.91 \times 10^9/L$  for death, respectively. Kaplan-Meier method showed chemotherapy-associated lymphopenia  $<0.66 \times 10^9/L$  was associated with shorter DFS (P < 0.0001), and chemotherapy-associated lymphopenia  $<0.91 \times 10^9/L$  was associated with shorter OS (P = 0.003). Cox regression model showed chemotherapy-associated lymphopenia  $<0.66 \times 10^9/L$  was the independent prognostic factor for DFS (HR, 3.521; 95%CI = 1.703-7.282), and chemotherapy-associated lymphopenia  $<0.91 \times 10^9/L$  was the independent prognostic factor for OS (HR, 2.083; 95% CI = 1.103-3.936). Multivariate logistic regression showed the risk of developing chemotherapy-associated lymphopenia  $<0.66 \times 10^9/L$  was found in those with pretreatment CEA  $\geq 10$  ng ml<sup>-1</sup> (OR, 3.338; 95% CI = 1.523-7.315), and the risk of developing chemotherapy-associated lymphopenia  $<0.91 \times 10^9/L$  was found in those with age >60 years (OR, 2.872; 95% CI = 1.344-6.136). CONCLUSIONS: Chemotherapy-associated lymphopenia  $<0.66 \times 10^9/L$  /  $<0.91 \times 10^9/L$  has a significant impact on the prognosis of CRC receiving adjuvant chemotherapy. Pretreatment CEA  $\geq 10$  ng ml<sup>-1</sup> is the independent risk factor for developing lymphopenia  $<0.66 \times 10^9/L$ , and age >60 years is the independent risk factor for developing lymphopenia  $<0.91 \times 10^9/L$  during adjuvant chemotherapy of CRC.

[1082]

**TÍTULO / TITLE:** - Differential regulation of microRNA-146a and microRNA-146b-5p in human retinal pigment epithelial cells by interleukin-1beta, tumor necrosis factor-alpha, and interferon-gamma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Vis. 2013 Apr 3;19:737-50. Print 2013.

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**RESUMEN / SUMMARY:** - PURPOSE: The inflammatory response of the retinal pigment epithelium (RPE) is implicated in the pathogenesis of age-related macular degeneration. The microRNAs miR-146a and miR-146b-5p can regulate the inflammatory process by attenuating cytokine signaling via the nuclear factor-kappaB pathway. The aim of the present study is to investigate the expression of miR-146a and miR-146b-5p in human RPE cells and their response to proinflammatory cytokines. METHODS: Confluent cultures of RPE

cells established from adult human donor eyes were treated with the proinflammatory cytokines interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-1beta. The expression of microRNAs was analyzed by real-time PCR using total RNA fraction. The retinal pigment epithelial cell line ARPE-19 was employed to analyze the promoter activity of the genes encoding miR-146a and miR-146b-5p. STAT1-binding activity of oligonucleotides was analyzed by electrophoretic mobility shift assay. ARPE-19 cells were transiently transfected with miR-146a and miR-146b-5p mimics for the analysis of IRAK1 expression by western immunoblotting. RESULTS: Real-time PCR analysis showed that miR-146a and 146b-5p are expressed in RPE cells. The cells responded to proinflammatory cytokines (IFN-gamma + TNF-alpha + IL-1beta) by highly increasing the expression of both miR-146a and miR-146b-5p. This was associated with an increase in the expression of transcripts for CCL2, CCL5, CXCL9, CXCL10, and IL-6, and a decrease in that for HMOX1. The miR-146a induction was more dependent on IL-1beta, since its omission from the cytokine mix resulted in a greatly reduced response. Similarly, the induction of miR-146b-5p was more dependent on IFN-gamma, since its omission from the cytokine mix minimized the effect. In addition, the increase in MIR146B promoter activity by the cytokine mix was effectively blocked by JAK inhibitor 1, a known inhibitor of the JAK/STAT signaling pathway. The expression of IRAK1 protein was decreased when ARPE-19 cells were transiently transfected with either miR-146a mimic or miR-146b-5p mimic. CONCLUSIONS: Our results clearly show that both miR-146a and miR-146b-5p are expressed in human RPE cells in culture and their expression is highly induced by proinflammatory cytokines (IFN-gamma + TNF-alpha + IL-1beta). The induction of miR-146a showed a dependency on IL-1beta, while that of miR-146b-5p on IFN-gamma. Our results show for the first time that miR-146b-5p expression is regulated by IFN-gamma, potentially via the JAK/STAT pathway. These two microRNAs could play a role in inflammatory processes underlying age-related macular degeneration or other retinal degenerative diseases through their ability to negatively regulate the nuclear factor-kappaB pathway by targeting the expression of IRAK1.

[1083]

**TÍTULO / TITLE:** - Interferon-gamma enhances phorbol myristate acetate-induced cell attachment and tumor necrosis factor production via the NF-kappaB pathway in THP-1 human monocytic cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Jun;7(6):1739-44. doi: 10.3892/mmr.2013.1419. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1419](#)

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**RESUMEN / SUMMARY:** - During inflammation, activated macrophages express adhesion molecules and produce cytokines that interact with other hematopoietic and stromal cells. THP-1 non-adherent human monocytic cells differentiate into plastic-adherent macrophages via alphaVbeta3 integrin, by ERK activation in the presence of phorbol myristate acetate (PMA). This has proven to be a valuable model for investigating functional monocyte/macrophage diversity. Interferon-gamma (IFN-gamma) is a Th1-cytokine that is crucial in macrophage activation. In this study, we investigated the effects of IFN-gamma on adhesion and the secretion of tumor necrosis factor (TNF) by PMA-stimulated THP-1 cells. IFN-gamma is incapable of inducing cell attachment and TNF production; however, it cumulatively upregulated PMA-induced basal adhesion and TNF production. IFN-gamma increased alphaV integrin, ICAM-1 and VCAM-1 expression and among these PMA-induced cell surface adhesion molecules, the blocking antibody for alphaV integrin suppressed adhesion and TNF production. Furthermore, IFN-gamma enhanced PMA-induced NF-kappaB phosphorylation and not ERK phosphorylation. Accordingly, the NF-kappaB pathway inhibitor (BAY 11-7082) inhibited the enhancing effect of IFN-gamma on adhesion and TNF production. By contrast, the MEK inhibitor (U0126) almost completely eliminated PMA-induced basal adhesion and TNF production. In conclusion, IFN-gamma regulates macrophage activation by mediating the NF-kappaB signaling pathway.

[1084]

**TÍTULO / TITLE:** - Efficacy and safety of albumin-bound paclitaxel in treating recurrent advanced non-small-cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin J Cancer Res. 2013 Apr;25(2):200-5. doi: 10.3978/j.issn.1000-9604.2013.03.04.

●●Enlace al texto completo (gratis o de pago) [3978/j.issn.1000-9604.2013.03.04](#)

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**INSTITUCIÓN / INSTITUTION:** - Cancer Institute and Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To observe the efficacy and safety of albumin-bound paclitaxel (ABP) monotherapy in treating recurrent advanced non-small-cell lung cancer (NSCLC). **METHODS:** We retrospectively analyzed the short-term efficacy and toxicities of ABP monotherapy in treating 21 patients who had previously undergone multiple cycles of therapy for their advanced NSCLC in our hospital since 2010. The treatment-related survival was also analyzed. **RESULTS:** Of these 21 patients, the best overall response was partial response (PR) in 6 patients (28.6%), stable disease (SD) in 10 patients (47.6%), and progressive disease (PD) in 5 patients (23.8%). The overall

response rate (ORR) was 28.6% and the disease control rate (DCR) (PR + SD) was 76.2%. The median progression-free survival (PFS) was 4.0 months (95% CI, 5.0-7.0 months). The main grade 3/4 toxicities included neutropenia (11.1%), peripheral nerve toxicity (5.6%), muscle and joint aches (5.6%), and fatigue (5.6%). CONCLUSIONS: The ABP monotherapy can achieve good objective response in advanced NSCLC patients who have previously received multiple cycles of treatment and be well tolerated.

[1085]

**TÍTULO / TITLE:** - ST6Gal-I sialyltransferase confers cisplatin resistance in ovarian tumor cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Ovarian Res. 2013 Apr 11;6(1):25. doi: 10.1186/1757-2215-6-25.

●●Enlace al texto completo (gratis o de pago) [1186/1757-2215-6-25](#)

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**RESUMEN / SUMMARY:** - BACKGROUND: Platinum drugs, including cisplatin, are a frontline therapeutic in ovarian cancer treatment and acquired resistance to these agents is a major contributor to ovarian cancer morbidity and mortality. In this study a novel glycosylation-dependent mechanism for cisplatin resistance is described. Specifically, cisplatin-induced cell death is blocked by the activity of the ST6Gal-I sialyltransferase. ST6Gal-I modifies specific receptors by adding a negatively charged sialic acid sugar which influences diverse receptor functions. Overexpression of ST6Gal-I is a hallmark of ovarian and other cancers and its expression has been correlated to metastasis and poor prognosis. METHODS: Tumor cell viability and apoptotic induction were determined in cell lines with ST6Gal-I overexpression and knockdown. In addition, cell populations with acquired resistance to cisplatin were assayed for endogenous ST6Gal-I expression. RESULTS: We show that forced expression of ST6Gal-I in OV4 ovarian cancer cells that lack endogenous ST6Gal-I causes reduced activation of caspase 3 and increased cell viability following cisplatin treatment. Conversely, forced ST6Gal-I knockdown in Pa-1 cells with high endogenous ST6Gal-I increases cisplatin-induced caspase activation and cell death. A2780 ovarian cancer cells selected for stable cisplatin resistance display upregulated endogenous ST6Gal-I when compared with parental, cisplatin-sensitive, A2780 cells. Similarly, extended low dose cisplatin treatment of a Pa-1 polyclonal ST6Gal-I shRNA knockdown population led to selection for subclones with elevated ST6Gal-I expression. CONCLUSIONS: Receptor sialylation by ST6Gal-I confers a survival advantage for tumor cells in the presence of cisplatin. These collective findings support a role for ST6Gal-I in

chemoresistance and highlight ST6Gal-I as a potential therapeutic target for platinum resistant tumors.

[1086]

**TÍTULO / TITLE:** - Zoledronic acid restores doxorubicin chemosensitivity and immunogenic cell death in multidrug-resistant human cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 12;8(4):e60975. doi: 10.1371/journal.pone.0060975. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060975](http://1371/journal.pone.0060975)

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**RESUMEN / SUMMARY:** - Durable tumor cell eradication by chemotherapy is challenged by the development of multidrug-resistance (MDR) and the failure to induce immunogenic cell death. The aim of this work was to investigate whether MDR and immunogenic cell death share a common biochemical pathway eventually amenable to therapeutic intervention. We found that mevalonate pathway activity, Ras and RhoA protein isoprenylation, Ras- and RhoA-downstream signalling pathway activities, Hypoxia Inducible Factor-1alpha activation were significantly higher in MDR+ compared with MDR- human cancer cells, leading to increased P-glycoprotein expression, and protection from doxorubicin-induced cytotoxicity and immunogenic cell death. Zoledronic acid, a potent aminobisphosphonate targeting the mevalonate pathway, interrupted Ras- and RhoA-dependent downstream signalling pathways, abrogated the Hypoxia Inducible Factor-1alpha-driven P-glycoprotein expression, and restored doxorubicin-induced cytotoxicity and immunogenic cell death in MDR+ cells. Immunogenic cell death recovery was documented by the ability of dendritic cells to phagocytise MDR+ cells treated with zoledronic acid plus doxorubicin, and to recruit anti-tumor cytotoxic CD8+ T lymphocytes. These data indicate that MDR+ cells have an hyper-active mevalonate pathway which is targetable with zoledronic acid to antagonize their ability to withstand chemotherapy-induced cytotoxicity and escape immunogenic cell death.

[1087]

**TÍTULO / TITLE:** - HnRNP A1/A2 and SF2/ASF Regulate Alternative Splicing of Interferon Regulatory Factor-3 and Affect Immunomodulatory Functions in Human Non-Small Cell Lung Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 29;8(4):e62729. doi: 10.1371/journal.pone.0062729. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062729](https://doi.org/10.1371/journal.pone.0062729)

**AUTORES / AUTHORS:** - Guo R; Li Y; Ning J; Sun D; Lin L; Liu X

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatrics, Peking University First Hospital, Beijing, China.

**RESUMEN / SUMMARY:** - Heterogeneous nuclear ribonucleoparticle A1/A2 (hnRNP A1/A2) and splicing factor 2/alternative splicing factor (SF2/ASF) are pivotal for precursor messenger RNA (pre-mRNA) splicing. Interferon regulatory factor-3 (IRF-3) plays critical roles in host defense against viral and microbial infection. Truncated IRF-3 proteins resulting from alternative splicing have been identified and characterized as functional antagonists to full-length IRF-3. In this study, we examined the molecular mechanism for splicing regulation of IRF-3 pre-mRNA and first reported the regulatory effect of hnRNP A1/A2 and SF2/ASF on IRF-3 splicing and activation. RNA interference-mediated depletion of hnRNP A1/A2 or SF2/ASF in human non-small cell lung cancer (NSCLC) cells increased exclusion of exons 2 and 3 of IRF-3 gene and reduced expression levels of IRF-3 protein and IRF-3 downstream effector molecules interferon-beta and CXCL10/IP-10. In addition, direct binding of hnRNP A1 and SF2/ASF to specific binding motifs in IRF-3 intron 1 was confirmed by RNA electrophoretic mobility shift assay. Subsequent minigene splicing assay showed that IRF-3 minigenes with mutated hnRNPA 1/A2 or SF2/ASF binding motifs increased exclusion of exons 2 and 3. Moreover, knockdown of hnRNP A1/A2 or SF2/ASF in NSCLC cells reinforced phytohemagglutinin-induced tumor necrosis factor-alpha release by peripheral blood mononuclear cells (PBMC) but suppressed that of interleukin-10 in NSCLC/PBMC co-cultures. Taken together, our results suggest that specific knockdown for hnRNP A1/A2 or SF2/ASF increase exclusion of exons 2 and 3 of IRF-3 pre-mRNA and influence immunomodulatory functions of human NSCLC cells.

[1088]

**TÍTULO / TITLE:** - Resistance to cisplatin-induced cell death conferred by the activity of organic anion transporting polypeptides (OATP) in human melanoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pigment Cell Melanoma Res. 2013 Apr 13. doi: 10.1111/pcmr.12108.

●●Enlace al texto completo (gratis o de pago) [1111/pcmr.12108](https://doi.org/10.1111/pcmr.12108)

**AUTORES / AUTHORS:** - Silvy F; Lissitzky JC; Bruneau N; Zucchini N; Landrier JF; Lombardo D; Verrando P

**INSTITUCIÓN / INSTITUTION:** - Aix-Marseille University, INSERM UMR911 (CRO2), Marseille, France.

**RESUMEN / SUMMARY:** - Expression of organic anion transporting polypeptides (OATP) transporters can be modified with potential incidence in cancers, yet they have not been considered in melanoma. Here, we demonstrate

transcriptional and protein expression of OATP members in human melanoma cell lines with sodium-independent organic anion uptake activity. Importantly, uptake of different organic anions over 24 h led to a common resistance signal to apoptotic cell death, induced further by cisplatin in 24 h. The mechanism is not dependent on the transport of cisplatin by the OATP, as it is not an OATP substrate. The resistance signal was modulated by PKC, disclosing it as signal mediator. This study suggests that OATP, which can be constantly activated by endobiotics, may contribute to melanoma chemotherapeutic resistance, thereby justifying the development of OATP targeting strategies.

[1089]

**TÍTULO / TITLE:** - The Efficacy of Lapatinib in Metastatic Breast Cancer with HER2 Non-Amplified Primary Tumors and EGFR Positive Circulating Tumor Cells: A Proof-Of-Concept Study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 7;8(5):e62543. doi: 10.1371/journal.pone.0062543. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062543](https://doi.org/10.1371/journal.pone.0062543)

**AUTORES / AUTHORS:** - Stebbing J; Payne R; Reise J; Frampton AE; Avery M; Woodley L; Di Leo A; Pestrin M; Krell J; Coombes RC

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Imperial College Healthcare National Health Service Trust, Charing Cross Hospital, London, United Kingdom.

**RESUMEN / SUMMARY:** - BACKGROUND: Analysis of circulating tumor cells (CTCs) provides real-time measures of cancer sub-populations with potential for CTC-directed therapeutics. We examined whether lapatinib which binds both HER2 and EGFR could induce depletion of the EGFR-positive pool of CTCs, which may in turn lead to clinical benefits. PATIENTS AND METHODS: Patients with metastatic breast cancer and HER2 non-amplified primary tumors with EGFR-positive CTCs were recruited and lapatinib 1500 mg daily was administered, in a standard two step phase 2 trial. RESULTS: There were no responses leading to termination at the first analysis with 16 patients recruited out of 43 screened. In 6 out of 14 (43%) individuals eligible for the efficacy analysis, a decrease in CTCs was observed with most of these having a greater decrease in their EGFR-positive CTC pool. CONCLUSIONS: This is one of the first studies of CTC-directed therapeutics and suggests that lapatinib monotherapy is not having any demonstrable clinical effects by reducing the EGFR-positive pool of CTCs in HER2 non-amplified primary tumors. Our attempt to expand the pool of patients eligible for a targeted therapy was unsuccessful; the role of clonal populations in cancer biology and therapeutic strategies to control them will require extensive evaluation in years to come. TRIAL REGISTRATION: Clinical trials.gov NCT00820924.

[1090]

**TÍTULO / TITLE:** - Endoplasmic reticulum stress plays a pivotal role in cell death mediated by the pan-deacetylase inhibitor panobinostat in human hepatocellular cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Transl Oncol. 2013 Apr;6(2):143-57. Epub 2013 Apr 1.

**AUTORES / AUTHORS:** - Montalbano R; Waldegger P; Quint K; Jabari S; Neureiter D; Illig R; Ocker M; Di Fazio P

**INSTITUCIÓN / INSTITUTION:** - Institute for Surgical Research, Philipps University of Marburg, Marburg, Germany.

**RESUMEN / SUMMARY:** - Panobinostat, a pan-deacetylase inhibitor, represents a novel therapeutic option for cancer diseases. Besides its ability to block histone deacetylases (HDACs) by promoting histone hyperacetylation, panobinostat interferes with several cell death pathways providing a potential efficacy against tumors. We have previously demonstrated that panobinostat has a potent apoptotic activity in vitro and causes a significant growth delay of hepatocellular carcinoma (HCC) tumor xenografts in nude mice models. Here, we show that treatment with panobinostat is able to induce noncanonical apoptotic cell death in HepG2 and in Hep3B cells, involving the endoplasmic reticulum (ER) stress by up-regulation of the molecular chaperone binding immunoglobulin protein/glucose-regulated protein 78, activation of eukaryotic initiation factor 2alpha-activating transcription factor 4 (tax-responsive enhancer element B67) and inositol requiring 1alpha-X-box binding protein 1 factors, strong increase and nuclear translocation of the transcription factor C/EBP homologous protein/growth arrest and DNA damage-inducible gene 153, and involvement of c-Jun N-terminal kinase. These signaling cascades culminate into the activation of the ER-located caspase-4/12 and of executioner caspases, which finally lead to cell demise. Our results clearly show that panobinostat induces an alternative ER stress-mediated cell death pathway in HCC cells, independent of the p53 status.

[1091]

**TÍTULO / TITLE:** - Jak2V617F myeloproliferative neoplasm stem cells and interferon-alpha.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncotarget. 2013 Apr;4(4):500-1.

**AUTORES / AUTHORS:** - Lane SW; Mullaly A

**INSTITUCIÓN / INSTITUTION:** - Queensland Institute of Medical Research, University of Queensland, Brisbane, Australia .

[1092]

**TÍTULO / TITLE:** - The Redox State of Cytochrome C Modulates Resistance to Methotrexate in Human MCF7 Breast Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 13;8(5):e63276. doi: 10.1371/journal.pone.0063276. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063276](https://doi.org/10.1371/journal.pone.0063276)

**AUTORES / AUTHORS:** - Barros S; Mencia N; Rodriguez L; Oleaga C; Santos C; Noe V; Ciudad CJ

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, School of Pharmacy, University of Barcelona, Barcelona, España ; Department of Biology, CESAM, University of Aveiro, Campus Universitario de Santiago, Aveiro, Portugal.

**RESUMEN / SUMMARY:** - BACKGROUND: Methotrexate is a chemotherapeutic agent used to treat a variety of cancers. However, the occurrence of resistance limits its effectiveness. Cytochrome c in its reduced state is less capable of triggering the apoptotic cascade. Thus, we set up to study the relationship among redox state of cytochrome c, apoptosis and the development of resistance to methotrexate in MCF7 human breast cancer cells. RESULTS: Cell incubation with cytochrome c-reducing agents, such as tetramethylphenylenediamine, ascorbate or reduced glutathione, decreased the mortality and apoptosis triggered by methotrexate. Conversely, depletion of glutathione increased the apoptotic action of methotrexate, showing an involvement of cytochrome c redox state in methotrexate-induced apoptosis. Methotrexate-resistant MCF7 cells showed increased levels of endogenous reduced glutathione and a higher capability to reduce exogenous cytochrome c. Using functional genomics we detected the overexpression of GSTM1 and GSTM4 in methotrexate-resistant MCF7 breast cancer cells, and determined that methotrexate was susceptible of glutathionylation by GSTs. The inhibition of these GSTM isoforms caused an increase in methotrexate cytotoxicity in sensitive and resistant cells. CONCLUSIONS: We conclude that overexpression of specific GSTMs, GSTM1 and GSTM4, together with increased endogenous reduced glutathione levels help to maintain a more reduced state of cytochrome c which, in turn, would decrease apoptosis, thus contributing to methotrexate resistance in human MCF7 breast cancer cells.

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[1093]

**TÍTULO / TITLE:** - Saikosaponin-d Enhances the Anticancer Potency of TNF-alpha via Overcoming Its Undesirable Response of Activating NF-Kappa B Signalling in Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:745295. doi: 10.1155/2013/745295. Epub 2013 Mar 12.

●●Enlace al texto completo (gratis o de pago) [1155/2013/745295](https://doi.org/10.1155/2013/745295)

**AUTORES / AUTHORS:** - Wong VK; Zhang MM; Zhou H; Lam KY; Chan PL; Law CK; Yue PY; Liu L

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Avenida Wai Long, Taipa, Macau, China.

**RESUMEN / SUMMARY:** - Tumor necrosis factor-alpha (TNF- alpha ) was reported as anticancer therapy due to its cytotoxic effect against an array of tumor cells. However, its undesirable responses of TNF- alpha on activating NF- kappa B signaling and pro-metastatic property limit its clinical application in treating cancers. Therefore, sensitizing agents capable of overcoming this undesirable effect must be valuable for facilitating the usage of TNF- alpha -mediated apoptosis therapy for cancer patients. Previously, saikosaponin-d (Ssd), a triterpene saponin derived from the medicinal plant, Bupleurum falcatum L. (Umbelliferae), showed to exhibit a variety of pharmacological activities such as antiinflammation, antibacteria, antiviral and anticancer. Recently, we found that Ssd could inhibit the activated T lymphocytes via suppression of NF- kappa B, NF-AT and AP-1 signaling. Here, we showed that Ssd significantly potentiated TNF- alpha -mediated cell death in HeLa and HepG2 cancer cells via suppression of TNF- alpha -induced NF- kappa B activation and its target genes expression involving cancer cell proliferation, invasion, angiogenesis and survival. Also, Ssd revealed a significant potency of abolishing TNF- alpha -induced cancer cell invasion and angiogenesis in HUVECs while inducing apoptosis via enhancing the loss of mitochondrial membrane potential in HeLa cells. Collectively, these findings indicate that Ssd has a significant potential to be developed as a combined adjuvant remedy with TNF- alpha for cancer patients.

[1094]

**TÍTULO / TITLE:** - Neoplastic-like transformation effect of single-walled and multi-walled carbon nanotubes compared to asbestos on human lung small airway epithelial cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nanotoxicology. 2013 May 28.

●●Enlace al texto completo (gratis o de pago)

[3109/17435390.2013.801089](https://doi.org/10.1080/310917435390.2013.801089)

**AUTORES / AUTHORS:** - Wang L; Stueckle TA; Mishra A; Derk R; Meighan T; Castranova V; Rojanasakul Y

**INSTITUCIÓN / INSTITUTION:** - HELD/PPRB, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA.

**RESUMEN / SUMMARY:** - Abstract Accumulating evidence indicates that carbon nanotubes (CNTs) are biopersistent and can cause lung damage. With similar fibrous morphology and mode of exposure to asbestos, a known human carcinogen, growing concern has arisen for elevated risk of CNT-induced lung carcinogenesis; however, relatively little is known about the long-term carcinogenic effect of CNT. Neoplastic transformation is a key early event leading to carcinogenesis. We studied the ability of single- and multi-walled

CNTs to induce neoplastic transformation of human lung epithelial cells compared to asbestos. Long-term (6-month) exposure of the cells to occupationally relevant concentrations of CNT in culture caused a neoplastic-like transformation phenotype as demonstrated by increased cell proliferation, anchorage-independent growth, invasion and angiogenesis. Whole-genome expression signature and protein expression analyses showed that single- and multi-walled CNTs shared similar signaling signatures which were distinct from asbestos. These results provide novel toxicogenomic information and suggest distinct particle-associated mechanisms of neoplasia promotion induced by CNTs and asbestos.

[1095]

**TÍTULO / TITLE:** - Lycopene and Beta-Carotene Induce Growth Inhibition and Proapoptotic Effects on ACTH-Secreting Pituitary Adenoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 7;8(5):e62773. doi: 10.1371/journal.pone.0062773. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062773](http://dx.doi.org/10.1371/journal.pone.0062773)

**AUTORES / AUTHORS:** - Haddad NF; Teodoro AJ; Leite de Oliveira F; Soares N; de Mattos RM; Hecht F; Dezone RS; Vairo L; Goldenberg RC; Gomes FC; de Carvalho DP; Gadelha MR; Nasciutti LE; Miranda-Alves L

**INSTITUCIÓN / INSTITUTION:** - Instituto de Ciencias Biomedicas, Universidade Federal do Rio de Janeiro, Brazil ; Servicio de Endocrinologia, Hospital Universitario Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brazil.

**RESUMEN / SUMMARY:** - Pituitary adenomas comprise approximately 10-15% of intracranial tumors and result in morbidity associated with altered hormonal patterns, therapy and compression of adjacent sella turcica structures. The use of functional foods containing carotenoids contributes to reduce the risk of chronic diseases such as cancer and vascular disorders. In this study, we evaluated the influence of different concentrations of beta-carotene and lycopene on cell viability, colony formation, cell cycle, apoptosis, hormone secretion, intercellular communication and expression of connexin 43, Skp2 and p27(kip1) in ACTH-secreting pituitary adenoma cells, the AtT20 cells, incubated for 48 and 96 h with these carotenoids. We observed a decrease in cell viability caused by the lycopene and beta-carotene treatments; in these conditions, the clonogenic ability of the cells was also significantly decreased. Cell cycle analysis revealed that beta-carotene induced an increase of the cells in S and G2/M phases; furthermore, lycopene increased the proportion of these cells in G0/G1 while decreasing the S and G2/M phases. Also, carotenoids induced apoptosis after 96 h. Lycopene and beta-carotene decreased the secretion of ACTH in AtT20 cells in a dose-dependent manner. Carotenoids blocked the gap junction intercellular communication. In addition, the treatments

increased the expression of phosphorylated connexin43. Finally, we also demonstrate decreased expression of S-phase kinase-associated protein 2 (Skp2) and increased expression of p27(kip1) in carotenoid-treated cells. These results show that lycopene and beta-carotene were able to negatively modulate events related to the malignant phenotype of AtT-20 cells, through a mechanism that could involve changes in the expression of connexin 43, Skp2 and p27(kip1); and suggest that these compounds might provide a novel pharmacological approach to the treatment of Cushing's disease.

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[1096]

**TÍTULO / TITLE:** - Personalized medicine: theranostics (therapeutics diagnostics) essential for rational use of tumor necrosis factor-alpha antagonists.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Discov Med. 2013 Apr;15(83):201-11.

**AUTORES / AUTHORS:** - Bendtzen K

**INSTITUCIÓN / INSTITUTION:** - Institute for Inflammation Research (IIR 7521), Rigshospitalet University Hospital, 9 Blegdamsvej, Copenhagen 2100, Denmark.

**RESUMEN / SUMMARY:** - With the discovery of the central pathogenic role of tumor necrosis factor (TNF)-alpha in many immunoinflammatory diseases, specific inhibition of this pleiotropic cytokine has revolutionized the treatment of patients with several non-infectious inflammatory disorders. As a result, genetically engineered anti-TNF-alpha antibody constructs now constitute one of the heaviest medicinal expenditures in many countries. All currently used TNF antagonists may dramatically lower disease activity and, in some patients, induce remission. Unfortunately, however, not all patients respond favorably, and safety can be severely impaired by immunogenicity, i.e., the ability of a drug to induce anti-drug antibodies (ADA). Assessment of ADA is therefore an important component of the evaluation of drug safety in both pre-clinical and clinical studies and in the process of developing less immunogenic and safer biopharmaceuticals. Therapeutics diagnostics, also called theranostics, i.e., monitoring functional drug levels and neutralizing ADA in the circulation, is central to more effective use of biopharmaceuticals. Hence, testing-based strategies rather than empirical dose-escalation may provide more cost-effective use of TNF antagonists as this allows therapies tailored according to individual requirements rather than the current universal approach to diagnosis. The objective of the present review is to discuss the reasons for recommending theranostics to implement an individualized use of TNF antagonists and to highlight some of the methodological obstacles that have obscured cost-effective ways of using these therapies.

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[1097]

**TÍTULO / TITLE:** - Appearance of ANCA - associated vasculitis under Tumor necrosis factor-alpha inhibitors treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Case Rep. 2013;14:80-2. doi: 10.12659/AJCR.883841. Epub 2013 Mar 20.

●●Enlace al texto completo (gratis o de pago) [12659/AJCR.883841](#)

**AUTORES / AUTHORS:** - Reitblat T; Reitblat O

**INSTITUCIÓN / INSTITUTION:** - Rheumatology Unit, Barsilai Medical Center, Ashkelon, Israel.

**RESUMEN / SUMMARY:** - BACKGROUND: Tumor necrosis factor-alpha inhibitors treatment is associated with several side effects. The most common are injection side reactions, headache, nausea and infections. The more rare are development of systemic autoimmune diseases. CASE REPORT: We describe two patients, who developed ANCA associated vasculitis during Tumor necrosis factor alpha inhibitors treatment. The diagnosis was confirmed by appropriate tissue picture, CT scan and laboratory findings. CONCLUSIONS: Our case series are unique, because vasculitis appeared after many years of the treatment and during complete patient's remission of their main illness.

[1098]

**TÍTULO / TITLE:** - Influence of Histone Deacetylase Inhibitors and DNA-Methyltransferase Inhibitors on the NK Cell-Mediated Lysis of Pediatric B-Lineage Leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Front Oncol. 2013 Apr 29;3:99. doi: 10.3389/fonc.2013.00099. Print 2013.

●●Enlace al texto completo (gratis o de pago) [3389/fonc.2013.00099](#)

**AUTORES / AUTHORS:** - Pfeiffer MM; Burow H; Schleicher S; Handgretinger R; Lang P

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Hematology and Oncology, University Children's Hospital, Eberhard Karls University Tuebingen Tuebingen, Germany.

**RESUMEN / SUMMARY:** - Epigenetic drugs like histone deacetylase inhibitors (HDACi) and DNA-methyltransferase inhibitors (DNMTi) have been shown to be effective against a variety of tumor entities. Among different molecular anticancer activities of epigenetic active substances, up-regulation of natural killer (NK) cell ligands was described to contribute to an enhanced NK cell-mediated killing of tumor cell lines. So far, no data is available on this effect in childhood acute lymphoblastic leukemia. We investigated the effect of two HDACi [vorinostat, valproic acid (VPA)] and two DNMTi (azacytidine, decitabine) on the viability, expression of NK ligands, and NK susceptibility of the pre-B-cell-ALL cell line MHH-CALL-4. Whereas vorinostat, azacytidine, and decitabine directly reduced viability of the cell line, VPA had no direct cytotoxic effect. NKG2D-ligands were expressed only at very low levels and not affected by epigenetic treatment. Higher expression was found for the DNAM-1 ligands with significant up regulation of CD112 after treatment with VPA (p = 0.02). No

significant increase in lysis mediated by resting NK cells could be observed, whereas incubation of target cells with decitabine resulted in a significant increase in lysis mediated by IL-2 activated NK cells ( $p = 0.0051$ ,  $p = 0.06$  for azacytidine). Vorinostat and VPA could increase the lysis by expanded NK cells which was statistically not significant due to high inter-individual variability. Furthermore, HDACi but not DNMTi reduced the NK-mediated lysis of MHH-CALL-4 after incubation of effector cells. In conclusion, there is a synergistic effect between epigenetic drugs and NK cells against MHH-CALL-4 which is not as strong as in other tumor entities. In situations where NK-mediated control of leukemia is assumed or wanted, a sophisticated combination of single epigenetic drugs and ex vivo expanded NK cells is needed to maximize the synergistic effect of both treatment strategies and DNMTIs may be preferred based on the direct inhibitory effect of HDACi on NK cell cytotoxicity.

[1099]

**TÍTULO / TITLE:** - Overexpression of retinoic acid-induced protein 3 predicts poor prognosis for hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1007/s12094-013-1040-](#)

[2](#)

**AUTORES / AUTHORS:** - Zheng J; Guo X; Gao X; Liu H; Tu Y; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Digestive Surgery, State Key Laboratory of Cancer Biology and Institute of Digestive Diseases, Xijing Hospital, Fourth Military Medical University, Xi'an, 710033, People's Republic of China.

**RESUMEN / SUMMARY:** - AIM: To investigate clinical significance of retinoic acid-induced protein 3 (RAI3) in hepatocellular carcinoma (HCC). METHODS: Expression of RAI3 at both mRNA and protein levels in tumor, para-tumor and normal liver tissues was detected in 106 HCC patients by real-time quantitative RT-PCR, Western blot and immunohistochemistry. Then, the correlation of RAI3 expression with clinicopathological characteristics and survivals of HCC patients was analyzed. RESULTS: Our data first found that RAI3 mRNA and protein expression were both significantly higher in HCC than in para-tumor (both  $P < 0.001$ ) and normal liver tissues (both  $P < 0.001$ ). The correlation analysis showed a positive correlation between RAI3 mRNA level and RAI3 protein level in HCC tissues ( $r = 0.8$ ,  $P < 0.001$ ). Immunohistochemistry data also revealed that overexpression of RAI3 was present in 73.6 % (78/106) of HCC tissues. In addition, high RAI3 protein expression was correlated with advanced TNM stage ( $P = 0.001$ ), high serum AFP ( $P = 0.008$ ), vascular invasion ( $P = 0.01$ ) and tumor recurrence ( $P = 0.008$ ). Moreover, HCC patients with overexpression of RAI3 had significantly shorter overall ( $P = 0.01$ ) and disease-free survival ( $P = 0.01$ ). Furthermore, multivariate analysis showed that overexpression of RAI3 was an independent prognostic factor for both overall

( $P = 0.02$ ) and disease-free survival ( $P = 0.03$ ) in HCC. CONCLUSION: Our data for the first time provide a basis for the concept that overexpression of RAI3 may contribute to the malignant progression of HCC and predict poor prognosis for patients with this deadly disease after curative hepatectomy. RAI3 might be an important marker for tumor progression and prognosis, as well as a potential therapeutic target of HCC.

[1100]

**TÍTULO / TITLE:** - C-reactive protein may be a prognostic factor in hepatocellular carcinoma with malignant portal vein invasion.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg Oncol. 2013 Apr 23;11:92. doi: 10.1186/1477-7819-11-92.

●●Enlace al texto completo (gratis o de pago) [1186/1477-7819-11-92](#)

**AUTORES / AUTHORS:** - Kim JM; Kwon CH; Joh JW; Ko JS; Park JB; Lee JH; Kim SJ; Paik SW; Park CK

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, #50 Ilwon-Dong Gangnam-Gu, Seoul, 135-710, Korea. [jw.joh@samsung.com](mailto:jw.joh@samsung.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Hepatocellular carcinoma (HCC) has a high predilection for portal vein invasion, and the prognosis of HCC with malignant portal vein invasion is extremely poor. The objective of this study was to investigate the outcomes and the prognostic factor of recurrence in HCC patients with malignant portal vein invasion. METHODS: We retrospectively reviewed the clinicopathologic data and outcomes of 83 HCC patients with malignant portal vein invasion and 1,056 patients without portal vein invasion who underwent liver resection. RESULTS: Increased serum alkaline phosphatase (ALP) levels, increased maximum tumor size, and intrahepatic metastasis were predisposing factors for malignant portal vein invasion by multivariate analysis. The median disease-free survival and overall survival of HCC patients with malignant portal vein invasion was 4.5 months and 25 months, respectively. The 1-year, 2-year, and 3-year disease-free survival rates were 30.6%, 26.1%, and 21.2%, respectively, and the overall survival rates for HCC patients with malignant portal vein invasion were 68.6%, 54.2%, and 41.6%, respectively. The initial detection site was the lung in HCC patients with portal vein invasion and the liver in HCC patients without portal vein invasion. C-reactive protein (CRP) was a significant independent predictor of tumor recurrence in HCC with malignant portal vein invasion after surgery. CONCLUSIONS: Increased ALP levels, increased maximum tumor size, and intrahepatic metastasis were independent predictors of malignant portal vein invasion in HCC. CRP level was closely associated with the predisposing factor of tumor recurrence in HCC patients with malignant portal vein invasion after a surgical resection, and lung metastasis was common.

[1101]

**TÍTULO / TITLE:** - Increased expression of pregnancy up-regulated non-ubiquitous calmodulin kinase is associated with poor prognosis in clear cell renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 25;8(4):e59936. doi: 10.1371/journal.pone.0059936. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0059936](#)

**AUTORES / AUTHORS:** - Wu S; Lv Z; Wang Y; Sun L; Jiang Z; Xu C; Zhao J; Sun X; Li X; Hu L; Tang A; Gui Y; Zhou F; Cai Z; Wang R

**INSTITUCIÓN / INSTITUTION:** - Institute of Immunology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China ; Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong, China ; Department of Urology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China.

**RESUMEN / SUMMARY:** - **PURPOSE:** The aims of this study were to evaluate the clinical significance and potential prognostic value of pregnancy up-regulated non-ubiquitous calmodulin kinase (PNCK) in clear cell renal cell carcinoma (ccRCC) patients. **MATERIALS AND METHODS:** The expression of PNCK mRNA was determined in 24 paired samples of ccRCCs and adjacent normal tissues using real-time RT-PCR. The expression of PNCK was determined in 248 samples of ccRCCs and 92 paired samples of adjacent normal tissues by immunohistochemical analysis. Statistical analysis was performed to define the relationship between PNCK expression and the clinical features of ccRCC. **RESULTS:** The mRNA level of PNCK was significantly higher in tumorous tissues than in the adjacent non-tumorous tissues ( $p < 0.001$ ). An immunohistochemical analysis of 92 paired tissue specimens showed that PNCK expression was higher in tumorous tissues than in the adjacent non-tumorous tissues ( $p < 0.001$ ). Moreover, there was a significant correlation between the PNCK expression and various clinicopathological parameters such as Fuhrman grade ( $p = 0.011$ ), tumor size ( $p < 0.001$ ), T stage ( $p < 0.001$ ) and N stage ( $p = 0.015$ ). Patients with higher PNCK expression had shorter overall survival time than those with lower PNCK expression ( $p < 0.001$ ). Multivariate analysis indicated that PNCK expression was an independent predictor for poor survival of ccRCC patients. **CONCLUSIONS:** To our knowledge, this is the first study that determines the relationship between PNCK and prognosis in ccRCC. We found that increased PNCK expression is associated with poor prognosis in ccRCC. PNCK may represent a novel prognostic marker for ccRCC.

[1102]

**TÍTULO / TITLE:** - Lentivirus-mediated RNA interference targeting the H19 gene inhibits cell proliferation and apoptosis in human choriocarcinoma cell line JAR.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cell Biol. 2013 May 27;14(1):26.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2121-14-26](https://doi.org/10.1186/1471-2121-14-26)

**AUTORES / AUTHORS:** - Yu LL; Chang K; Lu LS; Zhao D; Han J; Zheng YR; Yan YH; Yi P; Guo JX; Zhou YG; Chen M; Li L

**RESUMEN / SUMMARY:** - BACKGROUND: H19 is a paternally imprinted gene that has been shown to be highly expressed in the trophoblast tissue. Results from previous studies have initiated a debate as to whether noncoding RNA H19 acts as a tumor suppressor or as a tumor promoter in trophoblast tissue. In the present study, we developed lentiviral vectors expressing H19-specific small interfering RNA (siRNA) to specifically block the expression of H19 in the human choriocarcinoma cell line JAR. Using this approach, we investigated the impact of the H19 gene on the proliferation, invasion and apoptosis of JAR cells. Moreover, we examined the effect of H19 knockdown on the expression of insulin-like growth factor 2 (IGF2), hairy and enhancer of split homologue-1 (HES-1) and dual-specific phosphatase 5 (DUSP5) genes. RESULTS: H19 knockdown inhibited apoptosis and proliferation of JAR cells, but had no significant impact on cell invasion. In addition, H19 knockdown resulted in significant upregulation of HES-1 and DUSP5 expression, but not IGF2 expression in JAR cells. CONCLUSIONS: The finding that H19 downregulation could simultaneously inhibit proliferation and apoptosis of JAR cells highlights a putative dual function for H19 in choriocarcinoma and may explain the debate on whether H19 acts as a tumor suppressor or a tumor promoter in trophoblast tissue. Furthermore, upregulation of HES-1 and DUSP5 may mediate H19 downregulation-induced suppression of proliferation and apoptosis of JAR cells.

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[1103]

**TÍTULO / TITLE:** - Interferon-alpha Treatment for Growing Teratoma Syndrome of the Testis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Case Rep Nephrol Urol. 2013 Apr 10;3(1):40-5. doi: 10.1159/000350897. Print 2013 Jan.

●●Enlace al texto completo (gratis o de pago) [1159/000350897](https://doi.org/10.1159/000350897)

**AUTORES / AUTHORS:** - Inoue M; Hisasue S; Nagae M; China T; Saito K; Isotani S; Yamaguchi R; Ide H; Muto S; Horie S

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Teikyo University School of Medicine, Tokyo, Japan.

**RESUMEN / SUMMARY:** - A 23-year-old man with a right scrotal mass and back pain was referred for further treatment after right radical orchiectomy for testicular cancer. CT scans brought by the patient showed extensive metastasis to the retroperitoneal lymph nodes with no lung involvement. alpha-Fetoprotein and human chorionic gonadotropin were elevated preoperatively (384 ng/ml and 112 mIU/ml, respectively). Confirmation of the histopathologic examination revealed a mixed germ cell tumor (95% immature teratoma and 5% embryonal carcinoma). We started the patient on chemotherapy with bleomycin, etoposide,

and cisplatin (BEP). After a single course, tumor markers began to normalize, but there was radiologic evidence of continued growth of the retroperitoneal mass and new metastases in the lung. The patient was given 2 courses of salvage chemotherapy with etoposide, ifosfamide, and cisplatin (VIP). However, the mass and lung metastases continued to progress, and the patient was growing rapidly intolerant of the side effects of treatment (i.e., nausea, appetite loss, and pancytopenia). After thorough discussion with the patient and his family, we decided to start the patient on interferon (IFN)-alpha therapy. Natural, nonrecombinant IFN-alpha (OIF, Otsuka, Japan) 5,000,000 IU was administered twice weekly with approval of the ethics committee of our institution. The patient responded moderately with marked deceleration of tumor growth and stabilization of the lung metastases. He is alive and well at 16 months on IFN-alpha therapy.

[1104]

**TÍTULO / TITLE:** - Hemostatic absorbable gelatin sponge loaded with 5-fluorouracil for treatment of tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Nanomedicine. 2013;8:1499-506. doi: 10.2147/IJN.S41462. Epub 2013 Apr 18.

●●Enlace al texto completo (gratis o de pago) [2147/IJN.S41462](#)

**AUTORES / AUTHORS:** - Sun W; Chen Y; Yuan W

**INSTITUCIÓN / INSTITUTION:** - School of Pharmaceutical Sciences, Jilin University, Changchun, People's Republic of China.

**RESUMEN / SUMMARY:** - BACKGROUND: Surgical tumor resection is the main treatment for tumors however the treatment process often results in massive bleeding and tumor cell residue. The main aim of this research was to address problems such as bleeding, systemic chemotherapy side effects while enhancing quality of life, and increasing drug concentrations at the tumor site by developing a novel formulation with local long-term efficacy for treatment of tumors and to stop bleeding. METHODS: 5-Fluorouracil (5-FU) was suspended in an ethyl acetate solution of poly D,L-lactide-co-glycolic acid (PLGA) and a vacuum drying method was applied. The hemostatic gelatin sponge loaded with 5-FU was prepared by absorption of the suspension. The in vitro and in vivo characteristics of the hemostatic gelatin sponge loaded with 5-FU (5-FU-HAGS) were investigated. RESULTS: 5-FU-HAGS (hemostatic absorbable gelatin sponge loaded with 5-fluorouracil) was successfully produced with controlled release of the content and was reproducibly suitable for local tumor treatment as an implant to stop bleeding. The encapsulation efficiency of 5-FU-HAGS was above 98%. The in vitro 5-FU release kinetic profile matched a near zero-order equation for 20 days. The in vivo 5-FU plasma concentration was at a more stable level than when 5-FU solution was administered by subcutaneous injection. Bleeding can be stopped more effectively by coating a piece of blank gelatin sponge. The survival ratio of tumor-bearing mice using a 5-FU-HAGS

subcutaneous implant was higher when compared to mice given a subcutaneous injection of 5-FU solution. CONCLUSION: The 5-FU-HAGS system is a potential and effective way of enhancing the survival ratio and improving the quality of life of tumor-bearing mice.

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[1105]

**TÍTULO / TITLE:** - PTEN, Akt, MAPK, p53 and p95 expression to predict trastuzumab resistance in HER2 positive breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J BUON. 2013 Jan-Mar;18(1):44-50.

**AUTORES / AUTHORS:** - Duman BB; Sahin B; Acikalin A; Ergin M; Zorludemir S

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Cukurova University Medical Faculty, Adana, Turkey.

**RESUMEN / SUMMARY:** - Purpose: Mutations that activate the PIK3CA oncogene and inhibit the tumor suppressor gene PTEN action are commonly found in breast tumors. Akt is a key activator of cell survival. p53 is frequently found mutated in human tumors, and mutant p53 protein actively contributes to tumorigenesis. In selected cases of breast cancer, trastuzumab (TZMB) is incorporated in the primary treatment in the adjuvant and metastatic settings. Many studies have reported that selected patients are resistant to TZMB due to the presence of p95 HER2 fragments. To address this, we analysed PTEN, Akt, MAPK, p53 and p95 expression in breast cancer patients treated with TZMB. Methods: Out of 90 patients histologically diagnosed with breast cancer between 2004 and 2011, analysed were 25 patients with HER2 positive, and estrogen (ER) and progesterone receptors (PR) negative, metastatic or locally advanced disease. All 25 patients were treated with TZMB and resistance to TZMB was assessed. All patients were on anthracycline-and taxane-containing regimens. Tissue samples were obtained from paraffin blocks and evaluated immunohistochemically for PTEN, Akt, MAPK, p53, and p95 expression. Results: TZMB resistance was detected in 5 (20%) patients. Akt expression was positive in 2 patients (8%) and MAPK, p95, and p53 expression was positive in 1 patient (4%); PTEN expression was negative in 3 patients (12%). No significant differences were found between TZMB resistance and PTEN, Akt, MAPK, p53, and p95 expression. Subgroup analysis was carried out in the neoadjuvant treatment group. Complete pathologic response was detected in 3 patients (21.4%). Statistically significant differences were not found between the complete response rate and PTEN, Akt, MAPK, and p95 expression. There was a statistically significant correlation between p53 expression and complete pathologic response ( $p=0.02$ ). Conclusion: No statistically significant correlation between TZMB resistance and the expression of these biomarkers was noted. In patients with HER2-positive breast cancer that were treated with 4 dose-dense sequential cycles of doxorubicin and cyclophosphamide, followed by TZMB and paclitaxel combination therapy in the neoadjuvant setting, p53 expression could predict complete response to chemotherapy.

[1106]

**TÍTULO / TITLE:** - Predicting Pathologic Complete Response to neoadjuvant chemotherapy in breast cancer using Sparse Logistic Regression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Bioinform Res Appl. 2013;9(3):242-60. doi: 10.1504/IJBRA.2013.053605.

●●Enlace al texto completo (gratis o de pago)

[1504/IJBRA.2013.053605](#)

**AUTORES / AUTHORS:** - Hu W

**INSTITUCIÓN / INSTITUTION:** - Department of Computer Science, Houghton College, Houghton 14744, NY, USA.

**RESUMEN / SUMMARY:** - We utilised Sparse Logistic Regression (SLR) to build two sparse and interpretable predictors. The first one (SLR-65) was based on a signature consisting of the top 65 probe sets (59 genes) differentially expressed between Pathologic Complete Response (PCR) and Residual Disease (RD) cases, and the second one (SLR-Notch) was based on the genes involved in the Notch signaling related pathways (113 genes). The two predictors produced better predictions than the predictor in a previous study. The SLR-65 selected 16 informative genes and the SLR-Notch selected 12 informative genes.

[1107]

**TÍTULO / TITLE:** - The Difference in Prognostic Factors between Early Recurrence and Late Recurrence in Estrogen Receptor-Positive Breast Cancer: Nodal Stage Differently Impacts Early and Late Recurrence.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 22;8(5):e63510. doi: 10.1371/journal.pone.0063510. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0063510](#)

**AUTORES / AUTHORS:** - Ahn SG; Lee HM; Cho SH; Bae SJ; Lee SA; Hwang SH; Jeong J; Lee HD

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Yonsei University Medical College, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Probability of recurrence in patients with estrogen receptor (ER)-positive breast cancer remains constant for long periods. We compared tumor burden impact on late versus early recurrence in our cohort with long-term follow-up. METHODS: Five hundred and ninety five patients diagnosed with ER-positive breast cancer between 1989 and 2001 were classified into three groups: early recurrence within 5 years, late recurrence after 5 years, and no recurrence. We identified prognostic factors among the groups using logistic regression analysis. RESULTS: At median follow-up of 11.7 years, among 595 ER-positive women, 98 (16.4%) had early recurrence and 58 (9.7%) had late recurrence. On multivariate analysis, higher

nodal stage (N0 vs. N2, odds ratio [OR] 3.189; N0 vs. N3, OR 9.948), higher histologic grade (grade 1 vs. grade 2, OR 3.896; grade 1 vs. grade 3, OR 5.945), age >35 years (OR 0.295), and receiving endocrine therapy (OR 0.293) affected early recurrence. Compared to no recurrence, receiving endocrine therapy (OR 0.285) was solely related to decreased risk of late recurrence. Increased risk of early recurrence was noted with the higher nodal stage when early and no recurrences were compared. This phenomenon was not found in late recurrence. In the last comparison between the early and late recurrence, higher nodal stage (N0 vs. N3, OR 16.779) and higher histologic grade (grade 1 vs. grade 3, OR 18.111) repeatedly weighted for early recurrence. CONCLUSIONS: Nodal burden had an attenuated influence on late recurrence, which suggests that, unlike early recurrence, tumor biology might have a more important role than tumor load for late recurrence in ER-positive disease.

[1108]

**TÍTULO / TITLE:** - Association between SPARC mRNA Expression, Prognosis and Response to Neoadjuvant Chemotherapy in Early Breast Cancer: A Pooled in-silico Analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 26;8(4):e62451. doi: 10.1371/journal.pone.0062451. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062451](http://1371/journal.pone.0062451)

**AUTORES / AUTHORS:** - Azim HA Jr; Singhal S; Ignatiadis M; Desmedt C; Fumagalli D; Veys I; Larsimont D; Piccart M; Michiels S; Sotiriou C

**INSTITUCIÓN / INSTITUTION:** - Breast Cancer Translational Research Laboratory, J.C. Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium.

**RESUMEN / SUMMARY:** - INTRODUCTION: SPARC is an important regulator of the extracellular matrix and has been suggested to improve delivery of albumin-bound cytotoxics. However, little is known regarding its role in breast cancer (BC). METHODS: We conducted a pooled analysis of publically available datasets, in which BC patients who received no systemic therapy or received neoadjuvant chemotherapy were eligible. Patients were assigned to molecular subtypes using PAM-50. We computed a SPARC module (SPARC7), composed of genes with an absolute correlation with SPARC >0.7. In the systemically untreated cohort, we evaluated 1) expression of SPARC/SPARC7 according to breast cancer subtype, 2) association between SPARC/SPARC7 and biological processes related to proliferation, immune and stroma, and 3) association between SPARC/SPARC7 and relapse-free survival in a Cox model in all patients and in the different molecular subtypes adjusted for tumor size, nodal status, histological grade, and age. In the neoadjuvant cohort, we evaluated the association between SPARC and pCR in a logistic regression model, adjusted for the same clinicopathologic factors. RESULTS: 948 (10

datasets), and 791 (8 datasets) patients were included in the systemically untreated and neoadjuvant cohorts, respectively. High SPARC expression was associated with small tumor size, low histological grade and luminal-A tumors (all  $p < 0.0001$ ). There was a positive correlation between SPARC and stroma-related modules but negative correlation with proliferation modules. High SPARC expression was associated with poor prognosis in patients with basal and HER2+ breast cancer even after adjusting for clinicopathologic parameters. In the neoadjuvant cohort, a subgroup analysis suggested that high SPARC is associated with low rates of pCR in the HER2 subtype. Same results were observed on replacing SPARC by SPARC7. CONCLUSION: This analysis suggests a potential role of SPARC in determining prognosis and response to primary chemotherapy in early BC. This information could guide further development of albumin-bound cytotoxics in BC.

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[1109]

**TÍTULO / TITLE:** - Effect of aromatase inhibitors on bone mineral density in Japanese breast cancer population.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Drug Metab Pharmacokinet. 2013 Apr 9.

**AUTORES / AUTHORS:** - Akiyoshi T; Shimomura Y; Masuda S; Okamoto Y; Hiura S; Kato H; Asayama T; Ohtani H

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Pharmacy, Keio University.

**RESUMEN / SUMMARY:** - We retrospectively analyzed the bone mineral density (BMD) of postmenopausal Japanese women taking aromatase inhibitors (AIs), exemestane, anastrozole or letrozole calculated the decrease rate constant of BMD in each individual to compare the influence of three AIs on BMD. We also aimed to evaluate the preventive effect of bisphosphonates (BPs) on the AIs-induced decrease in BMD. The decrease rate constant of BMD ( $k_e$ ) in each individual was determined as a slope of linear regression of the relationship between time and logarithm of BMD value in each patient during the AI therapy. To compensate the age-related change in BMD level, we estimated the age-related decrease rate constant of BMD ( $k_{e,0}$ ) in healthy Japanese postmenopausal women from literature. AIs decreased BMD with  $k_e$  value of  $-0.0329 \text{ yr}^{-1}$ , which was 4.8-fold larger than  $k_{e,0}$  value of  $-0.0069 \text{ yr}^{-1}$ . No significant difference was detected in the influence on BMD among AIs. Co-administration of BP resumed the  $k_e$  value to  $-0.0117 \text{ yr}^{-1}$ , a value similar to  $k_{e,0}$ . The influence of AIs on BMD was quantitatively evaluated by using the decrease rate constant of BMD ( $k_e$ ). The present study also suggests that BPs may be useful to prevent the decrease in BMD induced by AIs.

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[1110]

**TÍTULO / TITLE:** - RNA interference-mediated USP22 gene silencing promotes human brain glioma apoptosis and induces cell cycle arrest.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1290-1294. Epub 2013 Feb 12.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1188](https://doi.org/10.3892/ol.2013.1188)

**AUTORES / AUTHORS:** - Li ZH; Yu Y; DU C; Fu H; Wang J; Tian Y

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, China-Japan Union Hospital of Jilin University, Changchun 130033;

**RESUMEN / SUMMARY:** - Ubiquitin-specific protease 22 (USP22) is a novel tumor stem cell marker that plays a key role in tumorigenesis and cell cycle progression. However, the effect of silencing the USP22 gene on human brain glioma cell growth is not well understood. In the present study, high gene expression of USP22 was identified in human brain glioma cells. In addition, RNA interference technology was used to silence USP22 gene expression in human brain glioma cells. Silencing the USP22 gene was found to effectively inhibit proliferation of human brain glioma cells, resulting in cell apoptosis and cell cycle arrest at the G2/M phase. USP22 silencing was also found to lead to reduced expression of cell cycle proteins, including CDK1, CDK2 and CyclinB1. In summary, in this study the USP22 gene was demonstrated to play a key regulatory role in the growth of human brain glioma cells by affecting progression of apoptosis and the cell cycle.

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[1111]

**TÍTULO / TITLE:** - A Prognosis Classifier for Breast Cancer Based on Conserved Gene Regulation between Mammary Gland Development and Tumorigenesis: A Multiscale Statistical Model.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(4):e60131. doi: 10.1371/journal.pone.0060131. Epub 2013 Apr 2.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060131](https://doi.org/10.1371/journal.pone.0060131)

**AUTORES / AUTHORS:** - Tian Y; Chen B; Guan P; Kang Y; Lu Z

**INSTITUCIÓN / INSTITUTION:** - Xiamen City Key Lab of Metabolism Disease & Metabolic Disease Research Center, Institute for Biomedical Research, Xiamen University, Xiamen, Fujian, China.

**RESUMEN / SUMMARY:** - Identification of novel cancer genes for molecular therapy and diagnosis is a current focus of breast cancer research. Although a few small gene sets were identified as prognosis classifiers, more powerful models are still needed for the definition of effective gene sets for the diagnosis and treatment guidance in breast cancer. In the present study, we have developed a novel statistical approach for systematic analysis of intrinsic correlations of gene expression between development and tumorigenesis in mammary gland. Based on this analysis, we constructed a predictive model for prognosis in breast cancer that may be useful for therapy decisions. We first defined developmentally associated genes from a mouse mammary gland epithelial gene expression database. Then, we found that the cancer modulated genes were enriched in this developmentally associated genes list.

Furthermore, the developmentally associated genes had a specific expression profile, which associated with the molecular characteristics and histological grade of the tumor. These result suggested that the processes of mammary gland development and tumorigenesis share gene regulatory mechanisms. Then, the list of regulatory genes both on the developmental and tumorigenesis process was defined an 835-member prognosis classifier, which showed an exciting ability to predict clinical outcome of three groups of breast cancer patients (the predictive accuracy 64 approximately 72%) with a robust prognosis prediction (hazard ratio 3.3 approximately 3.8, higher than that of other clinical risk factors (around 2.0-2.8)). In conclusion, our results identified the conserved molecular mechanisms between mammary gland development and neoplasia, and provided a unique potential model for mining unknown cancer genes and predicting the clinical status of breast tumors. These findings also suggested that developmental roles of genes may be important criteria for selecting genes for prognosis prediction in breast cancer.

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[1112]

**TÍTULO / TITLE:** - Identification of New Genes Downregulated in Prostate Cancer and Investigation of Their Effects on Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Test Mol Biomarkers. 2013 Apr 27.

●●Enlace al texto completo (gratis o de pago) [1089/gtmb.2012.0524](#)

**AUTORES / AUTHORS:** - Varisli L

**INSTITUCIÓN / INSTITUTION:** - Department of Biology, Art and Science Faculty, Harran University , Osmanbey Campus, Sanliurfa, Turkey .

**RESUMEN / SUMMARY:** - Prostate cancer is the most common noncutaneous malignant neoplasm in men in the Western countries. It is well established that genetic and epigenetic alterations are common events in prostate cancer, which may lead to aberrant expression of critical genes. Most of the studies are focused on the overexpressed or duplicated genes in prostate cancer. However, it is known that some of the differentially expressed genes in prostate cancer are downregulated. Since the inventory of downregulated genes is incomplete, we performed in silico approaches to reveal the novel prostate cancer downregulated genes. Moreover, we also investigated for a possible link between the expression of the downregulated genes and tumor grade, recurrence, metastasis, or survival status in prostate cancer. Our results showed that the expression of GSTP1 and AOX1 are downregulated in prostate cancer, in concordance with previous reports. Moreover, we showed that TPM2, CLU, and COL4A6 mRNA levels are downregulated in prostate cancer. Further, we found a significant negative correlation between the expression of the above-mentioned genes and the prognosis of prostate cancer.

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[1113]

**TÍTULO / TITLE:** - Prognostic value of MET, cyclin D1 and MET gene copy number in non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biomed Res. 2013 May;27(3):220-30. doi: 10.7555/JBR.27.20130004. Epub 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [7555/JBR.27.20130004](#)

**AUTORES / AUTHORS:** - Sun W; Song L; Ai T; Zhang Y; Gao Y; Cui J

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, the First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China.

**RESUMEN / SUMMARY:** - The aim of this study was to analyze the correlation of the expression of MET and cyclin D1 and MET gene copy number in non-small cell lung cancer (NSCLC) tissues and patient clinicopathologic characteristics and survival. Sixty-one NSCLC tissue specimens were included in the study. The expression of MET and cyclin D1 was evaluated by immunohistochemistry and MET gene copy number was assessed by quantitative real-time polymerase chain reaction (Q-PCR). Positive expression of MET and cyclin D1 protein and increased MET gene copy number occurred in 59.0%, 59.0% and 18.0% of 61 NSCLC tissues, respectively. MET-positivity correlated with poor differentiation ( $P = 0.009$ ). Increased MET gene copy number was significantly associated with lymph node metastasis ( $P = 0.004$ ) and advanced tumor stage ( $P = 0.048$ ), while the expression of cyclin D1 was not associated with any clinicopathologic parameters. There was a significant correlation between the expression of MET and MET gene copy number ( $P = 0.002$ ). Additionally, the expression of cyclin D1 had a significant association with the expression of MET as well as MET gene copy number ( $P = 0.002$  and  $P = 0.017$ , respectively). MET-positivity and increased MET gene copy number were significantly associated with poor overall survival ( $P = 0.003$  and  $P < 0.001$ , respectively) in univariate analysis. Multivariate Cox proportional hazard analysis confirmed that the expression of MET and MET gene copy number were prognostic indicators of NSCLC ( $P = 0.003$  and  $P = 0.001$ , respectively). The overexpression of MET and the increased MET gene copy number might be adverse prognostic factors for NSCLC patients. The activation of the MET/cyclin D1 signaling pathway may contribute to carcinogenesis and the development of NSCLC, and may represent a target for therapy.

[1114]

**TÍTULO / TITLE:** - PRC2 overexpression and PRC2-target gene repression relating to poorer prognosis in small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Sci Rep. 2013 May 29;3:1911. doi: 10.1038/srep01911.

●●Enlace al texto completo (gratis o de pago) [1038/srep01911](#)

**AUTORES / AUTHORS:** - Sato T; Kaneda A; Tsuji S; Isagawa T; Yamamoto S; Fujita T; Yamanaka R; Tanaka Y; Nukiwa T; Marquez VE; Ishikawa Y; Ichinose M; Aburatani H

**INSTITUCIÓN / INSTITUTION:** - 1] Genome Science Division, Research Center for Advanced Science and Technology (RCAST), The University of Tokyo, Japan  
[2] Department of Respiratory Medicine, Graduate School of Medicine, Tohoku University, Japan.

**RESUMEN / SUMMARY:** - Small cell lung cancer (SCLC) is a subtype of lung cancer with poor prognosis. Expression array analysis of 23 SCLC cases and 42 normal tissues revealed that EZH2 and other PRC2 members were highly expressed in SCLC. ChIP-seq for H3K27me3 suggested that genes with H3K27me3(+) in SCLC were extended not only to PRC2-target genes in ES cells but also to other target genes such as cellular adhesion-related genes. These H3K27me3(+) genes in SCLC were repressed significantly, and introduction of the most repressed gene JUB into SCLC cell line lead to growth inhibition. Shorter overall survival of clinical SCLC cases correlated to repression of JUB alone, or a set of four genes including H3K27me3(+) genes. Treatment with EZH2 inhibitors, DZNep and GSK126, resulted in growth repression of SCLC cell lines. High PRC2 expression was suggested to contribute to gene repression in SCLC, and may play a role in genesis of SCLC.

[1115]

**- CASTELLANO -**

**TÍTULO / TITLE:** beta-Catenin Ekspresyonunun Kolorektal Karsinomlarda Prognostik Parametreler ile İlişkisi.

**TÍTULO / TITLE:** - Relationship Between beta -Catenin Expression and Prognostic Parameters of Colorectal Carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Turk Patoloji Derg. 2013;29(2):87-93. doi: 10.5146/tjpath.2013.01157.

●●Enlace al texto completo (gratis o de pago) [5146/tjpath.2013.01157](#)

**AUTORES / AUTHORS:** - Peker K; Basoglu M; Gursan N

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Erzincan University, Faculty of Medicine, ERZINCAN, TURKEY.

**RESUMEN / SUMMARY:** - Objective: Colorectal carcinomas are the most frequent tumors of the gastrointestinal tract. beta-catenin, which is related to cadherins, is a cytoplasmic protein responsible for intercellular adhesion. It is also an important component in the Wnt signal pathway. Recent studies have shown structural alterations in the APC gene and axin in patients with colorectal carcinoma, along with beta-catenin. We aimed to compare beta-catenin expression, which is a prognostic factor itself, with other prognostic parameters. Material and Method: A total of 70 patients who had surgical intervention for colorectal malignancies between January 1994 and December

2003 were included in the study. Fifty-nine of the patients (84.3%) were male, 11 of the patients (15.7%) were female; their ages varied between 24 and 82 (mean 60.3 +/-15.2) years. Paraffin blocks were immunohistochemically stained for beta-catenin. The number of stained cell nuclei was assessed according to the stage of disease using the TNM classification, histological grade, lymphatic invasion, vascular invasion and tumor's local invasion. Results: When groups constituted according to tumor histologic grade were compared for prognostic parameters in terms of stain density for beta-catenin and number of stained cell nuclei, stain density was mild (+) and the number of stained nuclei was smaller in well-differentiated groups while stain density was strong (+++) and the number of stained nuclei was higher in poorly differentiated groups. There was a relation between beta-catenin expression and differentiation grade, lymph node metastasis, stage and tumor size but not with vascular invasion. Conclusion: These data indicate that beta-catenin, with functions in cell homeostasis and relations with the APC gene, has a substantial role in colorectal carcinogenesis.

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[1116]

**TÍTULO / TITLE:** - Cancer vaccines: Identification of biomarkers predictive of clinical efficacy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hum Vaccin Immunother. 2013 Apr 1;9(4).

**AUTORES / AUTHORS:** - Harrop R

**INSTITUCIÓN / INSTITUTION:** - Oxford BioMedica (UK) Ltd.; The Medawar Centre; Oxford, UK.

**RESUMEN / SUMMARY:** - Personalized medicine is playing an increasingly important role in the treatment of patients living with cancer. This landmark shift has been driven in part by statistics emerging from the "one size fits all" approach to the treatment of cancer patients. Some reports suggest that only a minority of individuals actually benefit from treatment and adverse effects of medications remain a major cause of hospitalization, morbidities and deaths. Although the side-effect profile of most immunotherapy treatment modalities is usually fairly benign, there is no reason to believe that immunotherapy is any different from other oncology therapies in that some patients are likely to receive more benefit than others. Indeed, the fact that generation of the therapeutic modality requires translation through multiple complex biological processes for an immunotherapy product to be effective may mean that such approaches require an even better understanding of the patient being treated. Furthermore, the very low success rate of cancer immunotherapy approaches to deliver benefit to patients demands a more detailed understanding of who will benefit and why. The identification of biomarkers predictive of treatment benefit is one route to improve the success rate of cancer vaccines.

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[1117]

**TÍTULO / TITLE:** - Evaluation of Argonaute protein as a predictive marker for human clear cell renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Exp Pathol. 2013 May 15;6(6):1086-94. Print 2013.

**AUTORES / AUTHORS:** - Li W; Liu M; Feng Y; Xu YF; Che JP; Wang GC; Zheng JH; Gao HJ

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Shanghai Tenth People's Hospital, Tongji University Shanghai, 200072, China.

**RESUMEN / SUMMARY:** - Argonaute subfamily proteins are involved in human organ growth and development. Recent studies found its association with human breast cancer, however, its expression profile and its prognostic value in clear cell renal cancer (ccRCC) have not been investigated. **METHODS:** Expression of the Argonaute proteins were assessed by immunohistochemistry (IHC) in tissue microarrays (TMA), containing paired tumor tissue and adjacent non-cancer tissue from 176 patients who had undergone surgery in hospital for histologically proven ccRCC. Prognostic value and correlation with other clinicopathologic factors were evaluated in two classifications. **RESULTS:** Data showed a significant higher expression of Argonaute 1 and Argonaute 2 present in neoplastic tissues compared with that in adjacent tissue; A significant correlation existed between the higher expression of Argonaute 1 protein with the T stage, lymph node metastasis and clinical TNM (cTNM); Survival analysis by Kaplan-Meier survival curve and log-rank test demonstrated that elevated Argonaute 1 and Argonaute 2 expression in cancer tissue predicted poorer overall survival (OS) compared with group in lower expression (36.3% VS 67.1%; 37.3% VS 53.9%; respectively). Notably, multivariate analyses by Cox's proportional hazard model revealed that expression of Argonaute 2 was an independent prognostic factor in renal cancer. **CONCLUSIONS:** In summary, our present study clarify that the aberrant expression of Argonaute in human RCC is possibly involved with tumorigenesis and development, and the Argonaute protein could act as a potential biomarker for prognosis assessment of renal cancer. Related mechanism is worthy of further investigation.

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[1118]

**TÍTULO / TITLE:** - Insulin-like growth factor-1 receptor (IGF-1R) as a biomarker for resistance to the tyrosine kinase inhibitor gefitinib in non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Oncol (Dordr). 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [1007/s13402-013-0133-](#)

[9](#)

**AUTORES / AUTHORS:** - Peled N; Wynes MW; Ikeda N; Ohira T; Yoshida K; Qian J; Ilouze M; Brenner R; Kato Y; Mascaux C; Hirsch FR

**INSTITUCIÓN / INSTITUTION:** - Departments of Medicine/Medical Oncology and Pathology, University of Colorado Cancer Center, UC Denver, 12801 E 17<sup>th</sup> Ave; Mail Stop 8177, Aurora, CO, 80045, USA, [nirp@post.tau.ac.il](mailto:nirp@post.tau.ac.il).

**RESUMEN / SUMMARY:** - BACKGROUND: The insulin-like growth factor-1 receptor (IGF-1R) pathway is known to play a role in the acquisition of resistance to epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). However, its exact role in TKI resistance has so far remained unclear. Here, we interrogated the hypothesis that the IGF-1R may serve as a biomarker for, and may play a role in, intrinsic resistance to the EGFR-specific TKI gefitinib in NSCLC. METHODS: Total-IGF-1R and phosphorylated (p)-IGF-1R expression levels were related to gefitinib sensitivity in 23 NSCLC cell lines. This sensitivity was re-evaluated after knocking down IGF-1R expression and after IGF-1R up-regulation through exogenous IGF-1 expression. The utility of IGF-1R expression as a predictive biomarker was also evaluated by immunohistochemistry (IHC) in 98 primary NSCLC samples from patients treated with gefitinib. RESULTS: Seventeen of the cell lines tested were resistant to gefitinib, whereas 3 cell lines were sensitive. The three remaining cell lines showed intermediate values. Thirteen resistant cell lines were found to be positive for total-IGF-1R expression, while all the sensitive cell lines were negative, resulting in a positive predictive value (PPV) of 81 % for total-IGF-1R to predict resistance. Seven resistant cell lines exhibited high p-IGF-1R levels, whereas all 3 sensitive cell lines were negative for p-IGF-1R, resulting in a PPV of 100 % for p-IGF-1R to predict resistance. Neither a knock-down of IGF-1R expression nor an activation of the IGF1-R pathway through exogenous IGF-1 expression affected gefitinib sensitivity. In primary NSCLC tissues, IGF-1R expression was found to be significantly higher in patients with progressive disease, i.e., showing gefitinib resistance, as compared to those with a complete or partial response. CONCLUSIONS: IGF-1R acts as a predictor for resistance to gefitinib in NSCLC cell lines and NSCLC patients, but does not seem to play a role in the intrinsic resistance to this drug. High total-IGF-1R and p-IGR-1R levels may predict such a resistance. Since the underlying mechanism does not appear to be related to proliferation induction, alternative pathways should be explored.

[1119]

**TÍTULO / TITLE:** - The Sensitivity of Diffuse Large B-Cell Lymphoma Cell Lines to Histone Deacetylase Inhibitor-Induced Apoptosis Is Modulated by BCL-2 Family Protein Activity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 7;8(5):e62822. doi: 10.1371/journal.pone.0062822. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062822](http://1371/journal.pone.0062822)

**AUTORES / AUTHORS:** - Thompson RC; Vardinogiannis I; Gilmore TD

**INSTITUCIÓN / INSTITUTION:** - Department of Biology, Boston University, Boston, Massachusetts, United States of America.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Diffuse large B-cell lymphoma (DLBCL) is a genetically heterogeneous disease and this variation can often be used to explain the response of individual patients to chemotherapy. One cancer therapeutic approach currently in clinical trials uses histone deacetylase inhibitors (HDACi's) as monotherapy or in combination with other agents. **METHODOLOGY/PRINCIPAL FINDINGS:** We have used a variety of cell-based and molecular/biochemical assays to show that two pan-HDAC inhibitors, trichostatin A and vorinostat, induce apoptosis in seven of eight human DLBCL cell lines. Consistent with previous reports implicating the BCL-2 family in regulating HDACi-induced apoptosis, ectopic over-expression of anti-apoptotic proteins BCL-2 and BCL-XL or pro-apoptotic protein BIM in these cell lines conferred further resistance or sensitivity, respectively, to HDACi treatment. Additionally, BCL-2 family antagonist ABT-737 increased the sensitivity of several DLBCL cell lines to vorinostat-induced apoptosis, including one cell line (SUDHL6) that is resistant to vorinostat alone. Moreover, two variants of the HDACi-sensitive SUDHL4 cell line that have decreased sensitivity to vorinostat showed up-regulation of BCL-2 family anti-apoptotic proteins such as BCL-XL and MCL-1, as well as decreased sensitivity to ABT-737. These results suggest that the regulation and overall balance of anti- to pro-apoptotic BCL-2 family protein expression is important in defining the sensitivity of DLBCL to HDACi-induced apoptosis. However, the sensitivity of DLBCL cell lines to HDACi treatment does not correlate with expression of any individual BCL-2 family member. **CONCLUSION/SIGNIFICANCE:** These studies indicate that the sensitivity of DLBCL to treatment with HDACi's is dependent on the complex regulation of BCL-2 family members and that BCL-2 antagonists may enhance the response of a subset of DLBCL patients to HDACi treatment.

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[1120]

**TÍTULO / TITLE:** - Expression of pAkt affects p53 codon 72 polymorphism-based prediction of response to radiotherapy in nasopharyngeal carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Radiat Oncol. 2013 May 11;8(1):117.

●●Enlace al texto completo (gratis o de pago) [1186/1748-717X-8-117](#)

**AUTORES / AUTHORS:** - Xie X; Wang H; Jin H; Ouyang S; Zhou J; Hu J; Xi X; Luo J; Zhang Y; Hu B

**RESUMEN / SUMMARY:** - **BACKGROUND:** Codon 72 (Arg/Pro), the most frequently studied single nucleotide polymorphism (SNP) of p53 to date, is associated with the ability of the gene to induce cell apoptosis. The PI3K/Akt pathway plays an essential role in the transcriptional activation function of p53, and is an important factor in radiotherapy resistance. The present study was designed to evaluate the prediction of response to radiotherapy based on p53

codon 72 SNP and pAkt expression in biopsy specimens of locoregional nasopharyngeal carcinoma (NPC) before treatment. Materials and methods: In total, 75 consecutive patients with locoregional NPC were enrolled. The p53 codon 72 SNP was identified from retrospectively collected paraffin-embedded biopsy specimens using Sanger sequencing. Expression patterns of p53, p21, 14-3-3sigma, and pAkt proteins were investigated using immunohistochemical analyses. The effects of genetic polymorphisms and protein expression on progression-free survival (PFS) were evaluated using the Cox proportional hazards model, Kaplan—Meier method, and log-rank test. RESULTS: The p53 codon 72 Pro/Pro carriers showed lower risk of disease progression (local recurrence and distant metastases) (HR: 0.300; 95% CI: 0.092--0.983; p=0.047). However, this association between the p53 codon 72 polymorphism and PFS was not significant in the pAkt-positive subgroup. No association was observed between protein expression of p53, p21 or 14-3-3sigma and p53 codon72 polymorphisms. Notably, positive expression of p53 protein appeared to be correlated with poorer PFS among patients diagnosed as local regional lymph node metastasis (N+) before treatment (p=0.032). CONCLUSIONS: The p53 codon 72 Pro/Pro genotype may be an effective independent prognostic marker for better outcome in patients with locoregional NPC. Based on the current findings, we hypothesize that pAkt weakens the predictive value of p53 codon 72 SNP in NPC. A combination of positive p53 protein expression and local regional lymph node metastasis may additionally be predictive of high risk of disease progression.

[1121]

**TÍTULO / TITLE:** - Lymphatic and Angiogenic Candidate Genes Predict the Development of Secondary Lymphedema following Breast Cancer Surgery.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 16;8(4):e60164. doi: 10.1371/journal.pone.0060164. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060164](#)

**AUTORES / AUTHORS:** - Miaskowski C; Dodd M; Paul SM; West C; Hamolsky D; Abrams G; Cooper BA; Elboim C; Neuhaus J; Schmidt BL; Smoot B; Aouizerat BE

**INSTITUCIÓN / INSTITUTION:** - Department of Physiological Nursing, University of California San Francisco, San Francisco, California, United States of America.

**RESUMEN / SUMMARY:** - The purposes of this study were to evaluate for differences in phenotypic and genotypic characteristics in women who did and did not develop lymphedema (LE) following breast cancer treatment. Breast cancer patients completed a number of self-report questionnaires. LE was evaluated using bioimpedance spectroscopy. Genotyping was done using a custom genotyping array. No differences were found between patients with (n = 155) and without LE (n = 387) for the majority of the demographic and clinical

characteristics. Patients with LE had a significantly higher body mass index, more advanced disease and a higher number of lymph nodes removed. Genetic associations were identified for four genes (i.e., lymphocyte cytosolic protein 2 (rs315721), neuropilin-2 (rs849530), protein tyrosine kinase (rs158689), vascular cell adhesion molecule 1 (rs3176861)) and three haplotypes (i.e., Forkhead box protein C2 (haplotype A03), neuropilin-2 (haplotype F03), vascular endothelial growth factor-C (haplotype B03)) involved in lymphangiogenesis and angiogenesis. These genetic associations suggest a role for a number of lymphatic and angiogenic genes in the development of LE following breast cancer treatment.

[1122]

**TÍTULO / TITLE:** - Are Agonistic Autoantibodies against G-Protein Coupled Receptors Involved in the Development of Long-Term Side Effects of Tumor Chemotherapy?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Case Rep Oncol. 2013 Jan;6(1):104-8. doi: 10.1159/000348425. Epub 2013 Feb 21.

●●Enlace al texto completo (gratis o de pago) [1159/000348425](#)

**AUTORES / AUTHORS:** - Haberland A; Santos RA; Schimke I; Wallukat G

**INSTITUCIÓN / INSTITUTION:** - Charite - Universitätsmedizin Berlin, Berlin, Germany.

**RESUMEN / SUMMARY:** - Metabolic syndrome and cardiomyopathies are long-term consequences of chemo- and radiotherapy and develop long after completing the initial tumor treatment. The slow progression of such late effects might be an indication of the involvement of autoimmune processes in the development of such follow-up consequences. Functionally active autoantibodies, which permanently stimulate relevant cell receptors, might be a crucial component. Here, we report the detection of functionally active agonistic autoantibodies such as the autoantibody against the adrenergic alpha1-receptor, the muscarinic M2-receptor, and the newly discovered autoantibody against the Mas-receptor in the plasma of a cancer survivor following chemotherapy treatment.

[1123]

**TÍTULO / TITLE:** - The acetone extract of Sclerocarya birrea (Anacardiaceae) possesses antiproliferative and apoptotic potential against human breast cancer cell lines (MCF-7).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - ScientificWorldJournal. 2013;2013:956206. doi: 10.1155/2013/956206. Epub 2013 Mar 20.

●●Enlace al texto completo (gratis o de pago) [1155/2013/956206](#)

**AUTORES / AUTHORS:** - Tanih NF; Ndip RN

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Microbiology, Faculty of Science and Agriculture, University of Fort Hare, P/Bag X1314, Alice 5700, South Africa.

**RESUMEN / SUMMARY:** - Interesting antimicrobial data from the stem bark of *Sclerocarya birrea*, which support its use in traditional medicine for the treatment of many diseases, have been delineated. The current study was aimed to further study some pharmacological and toxicological properties of the plant to scientifically justify its use. Anticancer activity of water and acetone extracts of *S. birrea* was evaluated on three different cell lines, HT-29, HeLa, and MCF-7 using the cell titre blue viability assay in 96-well plates. Apoptosis was evaluated using the acridine orange and propidium iodide staining method, while morphological structure of treated cells was examined using SEM. The acetone extract exhibited remarkable antiproliferative activities on MCF-7 cell lines at dose- and time-dependent manners (24 h and 48 h of incubation). The extract also exerted apoptotic programmed cell death in MCF-7 cells with significant effect on the DNA. Morphological examination also displayed apoptotic characteristics in the treated cells, including clumping, condensation, and culminating to budding of the cells to produce membrane-bound fragmentation, as well as formation of apoptotic bodies. The acetone extract of *S. birrea* possesses antiproliferative and apoptotic potential against MCF-7-treated cells and could be further exploited as a potential lead in anticancer therapy.

[1124]

**TÍTULO / TITLE:** - Arsenic Trioxide-Enhanced, Matrine-Induced Apoptosis in Multiple Myeloma Cell Lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Planta Med.* 2013 May 22.

●●Enlace al texto completo (gratis o de pago) [1055/s-0032-1328554](#)

**AUTORES / AUTHORS:** - Yu Q; Chen B; Zhang X; Qian W; Ye B; Zhou Y

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, The First Affiliated Hospital, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China.

**RESUMEN / SUMMARY:** - Matrine and arsenic trioxide are monomers used in traditional Chinese medicine possessing anti-myeloma activities. In this study, we evaluated the effects and mechanisms of matrine, arsenic trioxide, and their combination therapy on the proliferation and apoptosis of the myeloma cell lines RPMI8226 and U266. The effects of growth inhibition were measured by MTT, and apoptotic cells were analyzed by Hoechst 33258 staining and flow cytometry. The levels of caspase-3, poly (ADP-ribose) polymerase (a DNA repair enzyme), Bcl-2 and survivin (antiapoptotic signaling proteins), Bim (a proapoptotic signaling protein), total AKT, and phosphorylated AKT were evaluated by Western blot. Matrine significantly inhibited proliferation of RPMI8226 and U266 cell lines in a dose- and time-dependent manner with an IC50 at 24 h of 2.25 g/L and 2.18 g/L, and at 48 h of 1.64 g/L and 1.58 g/L,

respectively. Arsenic trioxide also displayed a dose- and time-dependent inhibition of growth of multiple myeloma cell lines, and synergistic effects occurred when the two were combined. Matriline (0.5, 1.0 g/L) and arsenic trioxide (2, 4 ug/mL) induced the apoptosis of myeloma cells; more early-stage apoptotic cells were seen with the combination therapy (matriline 0.5 g/L plus arsenic trioxide 2 ug/mL and matriline 1.0 g/L plus arsenic trioxide 4 ug/mL). Activation of caspase-3 and poly (ADP-ribose) polymerase, upregulation of Bim expression, downregulation of Bcl-2, survivin expression, as well as inhibition of phosphorylated AKT related to matriline (0, 0.25, 0.5, 1.0, and 2.0 g/L)-mediated apoptosis, and the effects were enhanced when arsenic trioxide (8 ug/mL) was combined with matriline (1.0 g/L). In conclusion, matriline displayed anti-myeloma effects through apoptotic induction, and arsenic trioxide had synergistic effects with matriline enhancing matriline-induced apoptosis.

[1125]

**TÍTULO / TITLE:** - Proinflammatory Cytokines and Bile Acids Upregulate DeltaNp73 Protein, an Inhibitor of p53 and p73 Tumor Suppressors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 22;8(5):e64306. doi: 10.1371/journal.pone.0064306. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064306](#)

**AUTORES / AUTHORS:** - Zaika E; Bhardwaj V; Wei J; Washington MK; Souza R; El-Rifai W; Zaika A

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, United States of America.

**RESUMEN / SUMMARY:** - Gastroesophageal reflux disease (GERD) is the main etiological factor behind the recent rapid increase in the incidence of esophageal adenocarcinoma. During reflux, esophageal cells are exposed to bile at low pH resulting in cellular damage and inflammation, which are known to facilitate cancer development. In this study, we investigated the regulation of p73 isoform, DeltaNp73alpha, in the reflux condition. Previous studies have reported that DeltaNp73 exhibits anti-apoptotic and oncogenic properties through inhibition of p53 and p73 proteins. We found that direct exposure of esophageal cells to bile acids in an acidic environment alters the phosphorylation of DeltaNp73, its subcellular localization and increases DeltaNp73 protein levels. Upregulation of DeltaNp73 was also observed in esophageal tissues collected from patients with GERD and Barrett's metaplasia, a precancerous lesion in the esophagus associated with gastric reflux. c-Abl, p38 MAPK, and IKK protein kinases were identified to interact in the regulation of DeltaNp73. Their inhibition with chemotherapeutic agents and siRNA suppresses DeltaNp73. We also found that pro-inflammatory cytokines, IL-

1beta and TNFalpha, are potent inducers of DeltaNp73alpha, which further enhance the bile acids/acid effect. Combined, our studies provide evidence that gastroesophageal reflux alters the regulation of oncogenic DeltaNp73 isoform that may facilitate tumorigenic transformation of esophageal metaplastic epithelium.

[1126]

**TÍTULO / TITLE:** - Prognostic Factors of Peritoneal Metastases from Colorectal Cancer following Cytoreductive Surgery and Perioperative Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - ScientificWorldJournal. 2013 Apr 18;2013:978394. doi: 10.1155/2013/978394. Print 2013.

●●Enlace al texto completo (gratis o de pago) [1155/2013/978394](#)

**AUTORES / AUTHORS:** - Yonemura Y; Canbay E; Ishibashi H

**INSTITUCIÓN / INSTITUTION:** - NPO to Support Peritoneal Surface Malignancy Treatment Unit, Peritoneal Carcinomatosis Center, Kishiwada Tokushukai and Kusatsu General Hospital, 1-26 Haruki-Moto-Machi, Kishiwada City, Osaka 596-0032, Japan.

**RESUMEN / SUMMARY:** - Background. Prolonged survival of patients affected by peritoneal metastasis (PM) of colorectal origin treated with complete cytoreduction followed by intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has been reported. However, two-thirds of the patients after complete cytoreduction and perioperative chemotherapy (POC) develop recurrence. This study is to analyze the prognostic factors of PM from colorectal cancer following the treatment with cytoreductive surgery (CRS) + POC. Patients and Methods. During the last 8 years, 142 patients with PM of colorectal origin have been treated with CRS and perioperative chemotherapy. The surgical resections consisted of a combination of peritonectomy procedures. Results. Complete cytoreduction (CCR-0) was achieved at a higher rate in patients with peritoneal cancer index (PCI) score less than 10 (94.7%, 71/75) than those of PCI score above 11 (40.2%, 37/67). Regarding the PCI of small bowel (SB-PCI), 89 of 94 (91.5%) patients with  $\leq 2$  and 22 of 48 (45.8%) patients with SB-PCI  $\geq 3$  received CCR-0 resection (P < 0.001). Postoperative Grade 3 and Grade 4 complications occurred in 11 (7.7%) and 14 (9.9%). The overall operative mortality rate was 0.7% (1/142). Cox hazard model showed that CCR-0, SB-PCI  $\leq 2$ , differentiated carcinoma, and PCI  $\leq 10$  were the independent favorite prognostic factors. Conclusions. Complete cytoreduction, PCI, SB-PCI threshold, and histologic type were the independent prognostic factors.

[1127]

**TÍTULO / TITLE:** - Taxane benefit in breast cancer-a role for grade and chromosomal stability.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nat Rev Clin Oncol. 2013 May 7;10(6):357-64. doi: 10.1038/nrclinonc.2013.67. Epub 2013 May 7.

●●Enlace al texto completo (gratis o de pago) [1038/nrclinonc.2013.67](https://doi.org/10.1038/nrclinonc.2013.67)

**AUTORES / AUTHORS:** - A'hern RP; Jamal-Hanjani M; Szasz AM; Johnston SR; Reis-Filho JS; Royle R; Swanton C

**INSTITUCIÓN / INSTITUTION:** - Cancer Research UK Section of Clinical Trials, The Institute of Cancer Research, 15 Cotswold Road, Belmont, Sutton SM2 5NG, UK.

**RESUMEN / SUMMARY:** - Chromosomal instability, which is a characteristic of many human cancers, contributes to intratumour heterogeneity and has been functionally implicated in resistance to taxane therapy in tumour models. However, defining the status of tumour chromosomal instability in a given tumour to test this hypothesis remains challenging. Measurements of numerical and structural chromosomal heterogeneity demonstrate that histological grade correlates with chromosomal instability in oestrogen receptor (ER)-positive breast cancer. Using data on adjuvant taxane therapy in women with breast cancer, we propose that patients with low-grade ER-positive tumours, which are thought to be chromosomally stable, might derive unexpected benefit from taxane therapy. We discuss the implications of the relationships between tumour grade, chromosomal instability and intratumour heterogeneity, the development of high-throughput methods to define tumour chromosomal instability and the potential use of chromosomal instability to tailor therapy.

[1128]

**TÍTULO / TITLE:** - Identification of HOXB8 and KLK11 expression levels as potential biomarkers to predict the effects of FOLFOX4 chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 May;9(5):727-36. doi: 10.2217/fon.13.25.

●●Enlace al texto completo (gratis o de pago) [2217/fon.13.25](https://doi.org/10.2217/fon.13.25)

**AUTORES / AUTHORS:** - Li S; Lu X; Chi P; Pan J

**INSTITUCIÓN / INSTITUTION:** - Department of Colorectal & Anal Surgery, Affiliated Union Hospital of Fujian Medical University, 29 Xinquan Road, Fuzhou, Fujian 350001, China.

**RESUMEN / SUMMARY:** - Aim: To measure global gene expression in primary advanced colorectal cancer patients who have undergone fluorouracil, leucovorin and oxaliplatin (FOLFOX4) chemotherapy and screen valuable biomarkers to predict the effects of chemotherapy. Materials & methods: Samples from primary advanced colorectal cancer patients were collected. The effects of chemotherapy were evaluated, and patients were divided into an experimental group and a control group. Cancerous tissue gene expression profiles were detected by chip technology. Valuable biomarkers were screened by bioinformatic analysis. Immunohistochemical analysis was performed to characterize the pattern of HOXB8 and KLK11 expression. HOXB8 and KLK11

signal probe values were analyzed using receiver operating characteristic analysis. Results: There were differentially expressed genes in the two groups. HOXB8 and KLK11 proteins were observed in the nucleus and on the outside of the cancer cells, respectively. Their prediction accuracies were 79.9 and 76.7%, respectively. Conclusion: HOXB8 and KLK11 may be classified as valuable biomarkers, as they can predict the effects of FOLFOX4 chemotherapy in primary advanced colorectal cancer patients.

[1129]

**TÍTULO / TITLE:** - Acetylcholine acts on androgen receptor to promote the migration and invasion but inhibit the apoptosis of human hepatocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 19;8(4):e61678. doi: 10.1371/journal.pone.0061678. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061678](http://1371/journal.pone.0061678)

**AUTORES / AUTHORS:** - Nie H; Cao Q; Zhu L; Gong Y; Gu J; He Z

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

**RESUMEN / SUMMARY:** - Hepatocellular carcinoma (HCC) is one of the most fatal cancers. In almost all populations, males have a higher HCC rate than females. Here we sought to explore the roles and mechanisms of acetylcholine (Ach) and androgen receptor (AR) on regulating the fate determinations of HCC. Ach activated AR and promoted its expression in HCC cells. Ach enhanced HCC cell migration and invasion but inhibited their apoptosis. Ach had no obvious effects on the migration, invasion, or apoptosis in AR-negative HCC cells. Elevation of migration and invasion induced by Ach was eliminated in AR-knockdown HCC cells. In contrast, Ach stimulated the migration and invasion but suppressed apoptosis in AR over-expressed HCC cells. Additionally, AR agonist R1881 promoted the migration and invasion but reduced the apoptosis of SNU-449 cells, whereas AR antagonist casodex inhibited the migration and invasion but stimulated the apoptosis of SNU-449 cells. STAT3 and AKT phosphorylation was activated by Ach in HCC cells. Collectively, these data suggest that Ach activates STAT3 and AKT pathways and acts on AR to promote the migration and invasion but inhibit the apoptosis of HCC cells. This study thus provides novel insights into carcinogenesis of liver cancer by local interaction between neurotransmitter Ach and hormone receptor AR in HCC.

[1130]

**TÍTULO / TITLE:** - Tumor marker carbohydrate antigen 125 predicts adverse outcome after transcatheter aortic valve implantation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - JACC Cardiovasc Interv. 2013 May;6(5):487-96. doi: 10.1016/j.jcin.2013.02.006.

●●Enlace al texto completo (gratis o de pago) [1016/j.jcin.2013.02.006](http://1016/j.jcin.2013.02.006)

**AUTORES / AUTHORS:** - Husser O; Nunez J; Nunez E; Holzamer A; Camboni D; Luchner A; Sanchis J; Bodi V; Riegger GA; Schmid C; Hilker M; Hengstenberg C

**INSTITUCIÓN / INSTITUTION:** - Klinik und Poliklinik für Innere Medizin II, University of Regensburg Medical Center, Regensburg, Germany; Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Munich, Germany.

**RESUMEN / SUMMARY:** - **OBJECTIVES:** This study sought to predict the value of tumor marker carbohydrate antigen 125 (CA125) before and after transcatheter aortic valve implantation (TAVI) for all-cause death and a composite endpoint of death, admission for heart failure, myocardial infarction, and stroke (major adverse cardiac events [MACE]). **BACKGROUND:** Risk stratification after TAVI remains challenging. The use of biomarkers in this setting represents an unmet need. **METHODS:** CA125 was measured in 228 patients before and after TAVI. The association with outcomes was assessed using parametric Cox regression and joint modeling for baseline and longitudinal analyses, respectively. CA125 was evaluated as logarithm transformation and dichotomized by its median value (M1  $\leq$ 15.7 U/ml vs. M2  $>$ 15.7 U/ml). **RESULTS:** At a median follow-up of 183 days (interquartile range: 63 to 365) and 144 days (interquartile range: 56 to 365), 50 patients (22%) died and 75 patients (33%) experienced MACE. A 3-fold increase in the rates for death and MACE was observed in patients above the median (M2 vs. M1) of CA125 (5.2 vs. 1.6 per 10 person-years and 8.3 vs. 3.3 per 10 person-years, respectively;  $p$  for both  $<$ 0.001). In a multivariable analysis adjusted for logistic EuroSCORE, New York Heart Association functional class III/IV, and device success, baseline values of CA125 (M2 vs. M1) independently predicted death (hazard ratio [HR]: 2.18; 95% confidence interval [CI]: 1.11 to 4.26;  $p = 0.023$ ) and MACE (HR: 1.77; 95% CI: 1.05 to 2.98;  $p = 0.031$ ). In the longitudinal analysis,  $\ln$ CA125 as a time-varying exposure, was highly associated with both endpoints: HR: 1.47; 95% CI: 1.01 to 2.14;  $p = 0.043$  and HR: 2.26; 95% CI: 1.28 to 3.98;  $p = 0.005$ , for death and MACE, respectively. **CONCLUSIONS:** Serum levels of CA125 before and after TAVI independently predict death and MACE.

[1131]

**TÍTULO / TITLE:** - A functional yeast survival screen of tumor-derived cDNA libraries designed to identify anti-apoptotic Mammalian oncogenes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 22;8(5):e64873. doi: 10.1371/journal.pone.0064873. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064873](http://1371/journal.pone.0064873)

**AUTORES / AUTHORS:** - Eissmann M; Schwamb B; Melzer IM; Moser J; Siele D; Kohl U; Rieker RJ; Wachter DL; Agaimy A; Herpel E; Baumgarten P; Mittelbronn M; Rakel S; Kogel D; Bohm S; Gutschner T; Diederichs S; Zornig M  
**INSTITUCIÓN / INSTITUTION:** - Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus, Frankfurt/Main, Germany.

**RESUMEN / SUMMARY:** - Yeast cells can be killed upon expression of pro-apoptotic mammalian proteins. We have established a functional yeast survival screen that was used to isolate novel human anti-apoptotic genes overexpressed in treatment-resistant tumors. The screening of three different cDNA libraries prepared from metastatic melanoma, glioblastomas and leukemic blasts allowed for the identification of many yeast cell death-repressing cDNAs, including 28% of genes that are already known to inhibit apoptosis, 35% of genes upregulated in at least one tumor entity and 16% of genes described as both anti-apoptotic in function and upregulated in tumors. These results confirm the great potential of this screening tool to identify novel anti-apoptotic and tumor-relevant molecules. Three of the isolated candidate genes were further analyzed regarding their anti-apoptotic function in cell culture and their potential as a therapeutic target for molecular therapy. PAICS, an enzyme required for de novo purine biosynthesis, the long non-coding RNA MALAT1 and the MAST2 kinase are overexpressed in certain tumor entities and capable of suppressing apoptosis in human cells. Using a subcutaneous xenograft mouse model, we also demonstrated that glioblastoma tumor growth requires MAST2 expression. An additional advantage of the yeast survival screen is its universal applicability. By using various inducible pro-apoptotic killer proteins and screening the appropriate cDNA library prepared from normal or pathologic tissue of interest, the survival screen can be used to identify apoptosis inhibitors in many different systems.

[1132]

**TÍTULO / TITLE:** - Mitoxantrone targets human ubiquitin-specific peptidase 11 (USP11) and is a potent inhibitor of pancreatic cancer cell survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Res. 2013 Jun 4.

●●Enlace al texto completo (gratis o de pago) [1158/1541-7786.MCR-12-0699](http://1158/1541-7786.MCR-12-0699)

**AUTORES / AUTHORS:** - Burkhart RA; Peng Y; Norris ZA; Tholey R; Talbott VA; Liang Q; Ai Y; Miller K; Lal S; Cozzitorto JA; Witkiewicz AK; Yeo CJ; Gehrman M; Napper A; Winter JM; Sawicki JA; Zhuang Z; Brody JR

**INSTITUCIÓN / INSTITUTION:** - Biliary, and Related Cancer Center, Thomas Jefferson University.

**RESUMEN / SUMMARY:** - Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related death in the United States with a 95% five-year mortality rate. For over a decade, gemcitabine (GEM) has been the established first-line treatment for this disease despite suboptimal response rates. The

development of PARP inhibitors that target the DNA damage repair mechanism in PDA cells has generated encouraging pre-clinical results. Ubiquitin-specific peptidase 11 (USP11), an enzyme that interacts with BRCA2, was recently discovered to play a key role in DNA double-strand break repair and may be a novel therapeutic target. Using a systematic high-throughput approach, we biochemically screened 2000 FDA approved and pharmacologically active compounds for inhibition of USP11 enzymatic activity. We identified six active small molecules that inhibit USP11 enzymatic activity. An in vitro drug sensitivity assay demonstrated that one of these USP11 inhibitors, mitoxantrone, affected PDA cell survival with an IC50 of less than 10 nM. Across six different PDA cell lines, two with defects in the Fanconi Anemia/BRCA2 pathway (Hs766T and Capan-1), mitoxantrone is 40 to 20,000-fold more potent than GEM, with increased endogenous USP11 mRNA levels associated with increased sensitivity to mitoxantrone. USP11 silencing in PDA cells also enhanced sensitivity to GEM. These findings establish a model for rapid discovery of FDA approved compounds by complementing in vitro biochemical experiments with cell culture studies. Further, they provide a strong rationale to study mitoxantrone in pre-clinical and early-phase clinical settings for the treatment of PDA.

[1133]

**TÍTULO / TITLE:** - GERD-Barrett-Adenocarcinoma: Do We Have Suitable Prognostic and Predictive Molecular Markers?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gastroenterol Res Pract. 2013;2013:643084. doi: 10.1155/2013/643084. Epub 2013 Mar 20.

●●Enlace al texto completo (gratis o de pago) [1155/2013/643084](#)

**AUTORES / AUTHORS:** - Illig R; Klieser E; Kiesslich T; Neureiter D

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, Paracelsus Medical University/Salzbürger Landeskliniken (SALK), Muellner HauptstraBe 48, 5020 Salzburg, Austria.

**RESUMEN / SUMMARY:** - Due to unfavorable lifestyle habits (unhealthy diet and tobacco abuse) the incidence of gastroesophageal reflux disease (GERD) in western countries is increasing. The GERD-Barrett-Adenocarcinoma sequence currently lacks well-defined diagnostic, progressive, predictive, and prognostic biomarkers (i) providing an appropriate screening method identifying the presence of the disease, (ii) estimating the risk of evolving cancer, that is, the progression from Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC), (iii) predicting the response to therapy, and (iv) indicating an overall survival-prognosis for EAC patients. Based on histomorphological findings, detailed screening and therapeutic guidelines have been elaborated, although epidemiological studies could not support the postulated increasing progression rates of GERD to BE and EAC. Additionally, proposed predictive and prognostic markers are rather heterogeneous by nature, lack substantial proofs, and

currently do not allow stratification of GERD patients for progression, outcome, and therapeutic effectiveness in clinical practice. The aim of this paper is to discuss the current knowledge regarding the GERD-BE-EAC sequence mainly focusing on the disputable and ambiguous status of proposed biomarkers to identify promising and reliable markers in order to provide more detailed insights into pathophysiological mechanisms and thus to improve prognostic and predictive therapeutic approaches.

[1134]

**TÍTULO / TITLE:** - Intravital FRET Imaging of Tumor Cell Viability and Mitosis during Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 15;8(5):e64029. doi: 10.1371/journal.pone.0064029. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064029](https://doi.org/10.1371/journal.pone.0064029)

**AUTORES / AUTHORS:** - Janssen A; Beerling E; Medema R; van Rheenen J

**INSTITUCIÓN / INSTITUTION:** - Division of Cell Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands ; Department of Medical Oncology and Cancer Genomics University Medical Center Utrecht, Utrecht, The Netherlands.

**RESUMEN / SUMMARY:** - Taxanes, such as docetaxel, are microtubule-targeting chemotherapeutics that have been successfully used in the treatment of cancer. Based on data obtained from cell cultures, it is believed that taxanes induce tumor cell death by specifically perturbing mitotic progression. Here, we report on data that suggest that this generally accepted view may be too simplified. We describe a high-resolution intravital imaging method to simultaneously visualize mitotic progression and the onset of apoptosis. To directly compare in vitro and in vivo data, we have visualized the effect of docetaxel on mitotic progression in mouse and human colorectal tumor cell lines both in vitro and in isogenic tumors in mice. We show that docetaxel-induced apoptosis in vitro occurs via mitotic cell death, whereas the vast majority of tumor cells in their natural environment die independent of mitotic defects. This demonstrates that docetaxel exerts its anti-tumor effects in vivo through means other than mitotic perturbation. The differences between in vitro and in vivo mechanisms of action of chemotherapeutics may explain the limited response to many of the anti-mitotic agents that are currently validated in clinical trials. Our data illustrate the requirement and power of our intravital imaging technique to study and validate the mode of action of chemotherapeutic agents in vivo, which will be essential to understand and improve their clinical efficacy.

[1135]

**TÍTULO / TITLE:** - High Serum CEA and CYFRA21-1 Levels after a Two-Cycle Adjuvant Chemotherapy for NSCLC: Possible Poor Prognostic Factors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Med. 2012 Dec;9(4):270-3. doi: 10.7497/j.issn.2095-3941.2012.04.009.

●●Enlace al texto completo (gratis o de pago) [7497/j.issn.2095-3941.2012.04.009](http://7497/j.issn.2095-3941.2012.04.009)

**AUTORES / AUTHORS:** - Lin XF; Wang XD; Sun DQ; Li Z; Bai Y

**INSTITUCIÓN / INSTITUTION:** - Tianjin Medical College, Tianjin 300222, China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** The aim of this study was to test whether carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (CYFRA21-1) can be used as a prognostic factor for non-small-cell lung cancer (NSCLC) after two cycles of adjuvant chemotherapy in NSCLC patients. **METHODS:** A total of 169 patients underwent at least two cycles of adjuvant chemotherapy. The serum levels of CEA and CYFRA21-1 were recorded after the second cycle of chemotherapy, and the patient follow-up was conducted. Overall survival (OS) and disease-free survival (DFS) were used as the primary endpoint and the secondary endpoint, respectively. **RESULTS:** The high levels of CEA and CYFRA21-1 after two cycles of adjuvant chemotherapy were poor prognostic factors for OS, with risk ratios (RR) of 2.003 and 1.702, respectively. A high CEA level was a poor prognostic factor (RR 1.152) for DFS. The median survival time (MST) of the high CEA level group was 26 months, whereas that of the normal group was 61 months ( $P<0.0001$ ). The median DFS time of the high CEA group and the normal group was 34 and 53 months, respectively ( $P<0.0001$ ). The MST of the high CYFRA21-1 group and the normal group was 43 and 56 months, respectively ( $P<0.0001$ ). **CONCLUSIONS:** The high serum levels of CEA or CYFRA21-1 after two cycles of adjuvant chemotherapy are poor prognostic factors for NSCLC patients.

[1136]

**TÍTULO / TITLE:** - UNC51-like kinase 1 as a potential prognostic biomarker for hepatocellular carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Exp Pathol. 2013;6(4):711-7. Epub 2013 Mar 15.

**AUTORES / AUTHORS:** - Xu H; Yu H; Zhang X; Shen X; Zhang K; Sheng H; Dai S; Gao H

**INSTITUCIÓN / INSTITUTION:** - Department of Hepatology, Taizhou People's Hospital, Jiangsu, China.

**RESUMEN / SUMMARY:** - Autophagy is a fundamental cell biological process that confers stress tolerance, limits damage, and sustains viability under adverse conditions. Defective autophagy is associated with diverse diseases. The study aimed to investigate the relationship between UNC51-like kinase 1 (ULK1) expression and clinicopathological characteristics as well as survival in patients with hepatocellular carcinoma (HCC). Expression levels of ULK1 in 55 paired HCC and paracancerous tissues were examined using immunohistochemistry. Although not statistically significant, the expression of ULK1 in adjacent

peritumoural tissue was lower than those in HCC tissues ( $P = 0.113$ ). Expression level of ULK1 was significantly associated with tumor size ( $P = 0.015$ ) after adjusted for age, sex, histologic grade, cirrhosis and TNM. Survival analysis showed that patients with high ULK1 expression had worse survival time than those with low ULK1 expression (hazard rate = 2.684, 95% CI 1.029-7.006,  $P = 0.044$ ). The findings of the present study provide evidence that ULK1 represents a potential novel prognostic biomarker for HCC patients and may play an important role during the progression of HCC.

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[1137]

**TÍTULO / TITLE:** - MiR-139 Inhibits Mcl-1 Expression and Potentiates TMZ-Induced Apoptosis in Glioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - CNS Neurosci Ther. 2013 Apr 2. doi: 10.1111/cns.12089.

●●Enlace al texto completo (gratis o de pago) [1111/cns.12089](#)

**AUTORES / AUTHORS:** - Li RY; Chen LC; Zhang HY; Du WZ; Feng Y; Wang HB; Wen JQ; Liu X; Li XF; Sun Y; Yang DB; Jiang T; Li YL; Jiang CL

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, China.

**RESUMEN / SUMMARY:** - AIMS: Mcl-1, an antiapoptotic member of the Bcl-2 family, is overexpressed in human glioblastoma, conferring a survival advantage to tumor cells. The mechanisms underlying its dysregulation have not been clarified. In this study, we explored the involvement of micro-RNAs that acted as endogenous sequence-specific suppressors of gene expression. METHODS AND RESULTS: Using computational and TCGA analysis, we identified miR-139 as being downregulated in glioblastoma in comparison with human brain tissue, as well as possessing a putative target site in Mcl-1 mRNA. Overexpression of miR-139 led to a clear decrease in Mcl-1 expression in gliomas. Reporter assays revealed direct post-transcriptional regulation involving miR-139 and the 3'-untranslated region of Mcl-1. Human glioma tissues with low expression of miR-139 displayed higher expression of Mcl-1 protein than those with high expression, suggesting that low miR-139 contributes to Mcl-1 overexpression. In addition, upregulation of miR-139 suppressed the proliferation and enhanced temozolomide (TMZ)-induced apoptosis. Finally, we observed that Mcl-1 knockdown resulted in similar effects compared with miR-139 transfection. CONCLUSION: Our results suggested that miR-139 negatively regulated Mcl-1 and induced apoptosis in cooperation with an anticancer drug TMZ in glioma.

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[1138]

**TÍTULO / TITLE:** - Oxaliplatin Plus 5-Fluorouracil and Folinic Acid (OFF) in Gemcitabine-Pretreated Advanced Pancreatic Cancer: A Phase II Study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gastrointest Cancer. 2013 Apr 19.

●●Enlace al texto completo (gratis o de pago) [1007/s12029-013-9495-](https://doi.org/10.1371/journal.pone.0060540)

[5](#)

**AUTORES / AUTHORS:** - El-Hadaad HA; Wahba HA

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt, [hend\\_am@mans.edu.eg](mailto:hend_am@mans.edu.eg).

**RESUMEN / SUMMARY:** - BACKGROUND: Despite median survival of less than 6 months, there is a significant proportion of advanced pancreatic cancer patients who progress on gemcitabine that remains fit, and these patients are candidates for second-line treatment. OBJECTIVE: The objective of this study is to evaluate the efficacy and safety of oxaliplatin plus 5-fluorouracil and folinic acid in patients with gemcitabine-pretreated advanced pancreatic cancer. PATIENTS AND METHODS: Thirty patients with advanced pancreatic cancer who were pretreated with gemcitabine received oxaliplatin (85 mg/m<sup>2</sup>) on days 1 and 15 followed by leucovorin (20 mg/m<sup>2</sup>) and 5-fluorouracil (500 mg/m<sup>2</sup>) on days 1, 8, and 15. The cycle was repeated every 3 weeks. RESULTS: The majority of patients (80 %) had locally advanced disease. Median age was 63 years, and 60 % were males. The liver was the most common site of metastasis. Partial response was observed in 2 patients (6.7 %) and stable disease in 6 patients (20 %), while 12 patients progressed (40 %). Improved performance status was reported in 10 patients (33.3 %). The median duration of response was 13 weeks, and median overall survival was 22 weeks. There was no grade 4 toxicity apart from grade 4 neutropenia in 6.6 % of patients. Neutropenia (46.5 %) and neuropathy (43.2 %) were the most common toxicities, while hand-foot syndrome was the least frequent one (20 %). There were no treatment-related deaths. The 6-month survival rate was 30 %. CONCLUSION: This regimen is feasible and active with an acceptable toxicity; however, further investigation in phase III trial is needed.

[1139]

**TÍTULO / TITLE:** - Phosphorylated I $\kappa$ B $\alpha$  predicts poor prognosis in activated B-cell lymphoma and its inhibition with thymoquinone induces apoptosis via ROS release.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e60540. doi: 10.1371/journal.pone.0060540. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060540](https://doi.org/10.1371/journal.pone.0060540)

**AUTORES / AUTHORS:** - Hussain AR; Uddin S; Ahmed M; Al-Dayel F; Bavi PP; Al-Kuraya KS

**INSTITUCIÓN / INSTITUTION:** - Human Cancer Genomic Research, Research Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

**RESUMEN / SUMMARY:** - Activated B-cell lymphoma (ABC), one of the three subtypes of Diffuse Large B-cell Lymphoma (DLBCL) has the worst survival rate after upfront chemotherapy and is characterized by constitutively activated NFkappaB. We therefore studied the role of NFkappaB in a cohort of clinical DLBCL samples and ABC cell lines. In our clinical tissue microarray cohort of DLBCL samples, p-IkappaBalpha was detected in 38.3% of ABC DLBCL and was an independent prognostic marker for poor survival. In vitro, we found that Thymoquinone (TQ), a natural compound isolated from *Nigella sativa* caused release of ROS in ABC cells. TQ-mediated release of ROS in turn inhibited NFkappaB activity by dephosphorylating IkappaBalpha and decreased translocation of p65 subunit of NFkappaB in the nuclear compartment in ABC cell lines. This led to inhibition of cell viability and induction of mitochondrial dependent apoptosis in ABC-DLBCL cell lines. Additionally, TQ treatment also caused up-regulation of death receptor 5 (DR5), however, up-regulation of DR5 did not play a role in TQ-induced apoptosis. Finally, combination of sub-optimal doses of TQ and TRAIL induced efficient apoptosis in ABC-DLBCL cell lines. These data show that p-IkappaBalpha can be used as a prognostic marker and target for therapy in this aggressive sub-type of DLBCL and TQ may play an important role in the management of DLBCL in the future.

[1140]

**TÍTULO / TITLE:** - Resveratrol 3-O-d-glucuronide and resveratrol 4'-O-d-glucuronide inhibit colon cancer cell growth: Evidence for a role of A3 adenosine receptors, cyclin D1 depletion, and G1 cell cycle arrest.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Nutr Food Res. 2013 May 7. doi: 10.1002/mnfr.201200742.

●●Enlace al texto completo (gratis o de pago) [1002/mnfr.201200742](http://1002/mnfr.201200742)

**AUTORES / AUTHORS:** - Polycarpou E; Meira LB; Carrington S; Tyrrell E; Modjtahedi H; Carew MA

**INSTITUCIÓN / INSTITUTION:** - School of Pharmacy and Chemistry, Kingston University, Kingston upon Thames, UK.

**RESUMEN / SUMMARY:** - SCOPE: Resveratrol is a plant-derived polyphenol with chemotherapeutic properties in animal cancer models and many biochemical effects in vitro. Its bioavailability is low and raises the possibility that the metabolites of resveratrol have biological effects. Here we investigate the actions of resveratrol 3-O-d-glucuronide, resveratrol 4'-O-d-glucuronide, and resveratrol 3-O-d-sulfate on the growth of colon cancer cells in vitro. METHODS AND RESULTS: The growth of Caco-2, HCT-116, and CCL-228 cells was measured using the neutral red and MTT assays. Resveratrol and each metabolite inhibited cell growth with IC50 values of 9.8-31 μM. Resveratrol caused S phase arrest in all three cell lines. Resveratrol 3-O-d-glucuronide and resveratrol 4'-O-d-glucuronide caused G1 arrest in CCL-228 and Caco-2 cells. Resveratrol 3-O-d-sulfate had no effect on cell cycle. Growth inhibition was

reversed by an inhibitor of AMP-activated protein kinase (compound C) or an adenosine A3 receptor antagonist (MRS1191). The A3 receptor agonist 2Cl-IB-MECA inhibited growth and A3 receptors were detected in all cell lines. The resveratrol glucuronides also reduced cyclin D1 levels but at higher concentrations than in growth experiments and generally did not increase phosphorylated AMP-activated protein kinase. CONCLUSION: Resveratrol glucuronides inhibit cell growth by G1 arrest and cyclin D1 depletion, and our results strongly suggest a role for A3 adenosine receptors in this inhibition.

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[1141]

**TÍTULO / TITLE:** - Deja Vu: EGF Receptors Drive Resistance to BRAF Inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Discov. 2013 May;3(5):487-90. doi: 10.1158/2159-8290.CD-13-0131.

●●Enlace al texto completo (gratis o de pago) [1158/2159-8290.CD-13-0131](#)

**AUTORES / AUTHORS:** - Girotti MR; Marais R

**INSTITUCIÓN / INSTITUTION:** - Molecular Oncology Group, The Paterson Institute for Cancer Research, The University of Manchester, Manchester, United Kingdom.

**RESUMEN / SUMMARY:** - Summary: The promise of personalized medicine is upon us, and in some cancers, targeted therapies are rapidly becoming the mainstay of treatment for selected patients based on their molecular profile. The protein kinase BRAF is a driver oncogene in both thyroid cancer and melanoma, but while drugs that target BRAF and its downstream signaling pathway are effective in melanoma, they are ineffective in thyroid cancer. In this issue of Cancer Discovery, Montero-Conde and colleagues investigate why thyroid cancer is resistant to BRAF inhibitors despite the presence of BRAF mutation. Cancer Discov; 3(5); 487-90. ©2013 AACR.

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[1142]

**TÍTULO / TITLE:** - Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4-ALK-rearranged non-small-cell lung cancer harbored coexisting EGFR mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 May 29;13:262. doi: 10.1186/1471-2407-13-262.

●●Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-262](#)

**AUTORES / AUTHORS:** - Miyanaga A; Shimizu K; Noro R; Seike M; Kitamura K; Kosaihiira S; Minegishi Y; Shukuya T; Yoshimura A; Kawamoto M; Tsuchiya S; Hagiwara K; Soda M; Takeuchi K; Yamamoto N; Mano H; Ishikawa Y; Gemma A

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan.  
[agemma@nms.ac.jp](mailto:agemma@nms.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The EML4-ALK (echinoderm microtubule-associated protein-like 4 gene and the anaplastic lymphoma kinase gene) fusion oncogene represents a novel molecular target in a small subset of non-small-cell lung cancers (NSCLCs). The EML4-ALK fusion gene occurs generally in NSCLC without mutations in epidermal growth factor receptor (EGFR) and KRAS. CASE PRESENTATION: We report that a case of EML4-ALK-positive NSCLC with EGFR mutation had a response of stable disease to both an EGFR tyrosine kinase inhibitor (EGFR-TKI) and ALK inhibitor. CONCLUSIONS: We described the first clinical report of a patient with EML4-ALK-positive NSCLC with EGFR mutation that had a response of stable disease to both single-agent EGFR-TKI and ALK inhibitor. EML4-ALK translocation may be associated with resistance to EGFR-TKI, and EGFR signaling may contribute to resistance to ALK inhibitor in EML4-ALK-positive NSCLC.

[1143]

**TÍTULO / TITLE:** - Identifying resistance mechanisms against five tyrosine kinase inhibitors targeting the ERBB/RAS pathway in 45 cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e59503. doi: 10.1371/journal.pone.0059503. Epub 2013 Mar 29.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0059503](https://doi.org/10.1371/journal.pone.0059503)

**AUTORES / AUTHORS:** - Penzvalto Z; Tegze B; Szasz AM; Sztupinszki Z; Liko I; Szendroi A; Schafer R; Gyorffy B

**INSTITUCIÓN / INSTITUTION:** - 1<sup>st</sup> Department of Pediatrics, Semmelweis University, Budapest, Hungary.

**RESUMEN / SUMMARY:** - Because of the low overall response rates of 10-47% to targeted cancer therapeutics, there is an increasing need for predictive biomarkers. We aimed to identify genes predicting response to five already approved tyrosine kinase inhibitors. We tested 45 cancer cell lines for sensitivity to sunitinib, erlotinib, lapatinib, sorafenib and gefitinib at the clinically administered doses. A resistance matrix was determined, and gene expression profiles of the subsets of resistant vs. sensitive cell lines were compared. Triplicate gene expression signatures were obtained from the caArray project. Significance analysis of microarrays and rank products were applied for feature selection. Ninety-five genes were also measured by RT-PCR. In case of four sunitinib resistance associated genes, the results were validated in clinical samples by immunohistochemistry. A list of 63 top genes associated with resistance against the five tyrosine kinase inhibitors was identified. Quantitative RT-PCR analysis confirmed 45 of 63 genes identified by microarray analysis.

Only two genes (ANXA3 and RAB25) were related to sensitivity against more than three inhibitors. The immunohistochemical analysis of sunitinib-treated metastatic renal cell carcinomas confirmed the correlation between RAB17, LGALS8, and EPCAM and overall survival. In summary, we determined predictive biomarkers for five tyrosine kinase inhibitors, and validated sunitinib resistance biomarkers by immunohistochemistry in an independent patient cohort.

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[1144]

**TÍTULO / TITLE:** - Prognostic significance of biological apoptosis factors in gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J BUON. 2013 Jan-Mar;18(1):138-46.

**AUTORES / AUTHORS:** - Sezer C; Yildirim M; Yildiz M; Sezgin A; Donem Dilli U; Goktas S; Bulbuller N

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Antalya Education and Research Hospital, Antalya, Turkey.

**RESUMEN / SUMMARY:** - Purpose: Gastric cancer is a biologically heterogeneous disease containing many genetic and epigenetic alterations. In our study, the expression status of apoptosis-inducing p53 and apoptosis-inhibiting Bcl-2 in gastric cancer and their relation with prognosis, if any, was investigated.

Methods: Patients that were being followed in our clinic and had histopathologically diagnosed gastric adenocarcinoma were included in this study. The p53 and bcl-2 expressions were investigated immunohistochemically and patients were grouped according to p53 and Bcl-2 expression as follows: group A: both p53 and Bcl-2 negative; group B: p53 positive and Bcl-2 negative; group C: p53 negative and Bcl-2 positive; group D: both p53 and Bcl-2 positive. Results: In 19 (51.4%) patients positive immunostaining with p53 was observed, while negative in 18 (48.6%). A significant relationship between the metastatic ability of the tumor and p53 expression was determined ( $p=0.004$ ). In 78.6% of the metastatic tumors no p53 expression was observed, while in 69.6% of the non-metastatic tumors p53 expression was positive. No significant relationship was detected between p53 expression and survival. Positive immunostaining with Bcl-2 was observed in 9 (16.7%) patients, and negative in 45 (83.3%). No significant relationship was determined between the Bcl-2 expression and the depth of invasion, dissemination to lymph nodes and metastatic ability of the tumor. A borderline statistically significant relationship was determined between the Bcl-2 expression and survival ( $p=0.051$ ). Group B patients showed a statistically significant survival difference compared with the other groups ( $p=0.022$ ). Conclusion: The results of this study suggest that concurrent evaluation of p53 and Bcl-2 in patients with gastric adenocarcinoma may have prognostic importance.

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[1145]

**TÍTULO / TITLE:** - Comparison of prognostic genomic predictors in colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 23;8(4):e60778. doi: 10.1371/journal.pone.0060778. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060778](#)

**AUTORES / AUTHORS:** - Park YY; Lee SS; Lim JY; Kim SC; Kim SB; Sohn BH; Chu IS; Oh SC; Park ES; Jeong W; Kim SS; Kopetz S; Lee JS

**INSTITUCIÓN / INSTITUTION:** - Departments of Systems Biology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America.

**RESUMEN / SUMMARY:** - BACKGROUND: Although several prognostic genomic predictors have been identified from independent studies, it remains unclear whether these predictors are actually concordant with respect to their predictions for individual patients and which predictor performs best. We compared five prognostic genomic predictors, the V7RHS, the ColoGuideEx, the Meta163, the OncoDX, and the MDA114, in terms of predicting disease-free survival in two independent cohorts of patients with colorectal cancer.

STUDY DESIGN: Using original classification algorithms, we tested the predictions of five genomic predictors for disease-free survival in two cohorts of patients with colorectal cancer (n = 229 and n = 168) and evaluated concordance of predictors in predicting outcomes for individual patients.

RESULTS: We found that only two predictors, OncoDX and MDA114, demonstrated robust performance in identifying patients with poor prognosis in 2 independent cohorts. These two predictors also had modest but significant concordance of predicted outcome (r>0.3, P<0.001 in both cohorts).

CONCLUSIONS: Further validation of developed genomic predictors is necessary. Despite the limited number of genes shared by OncoDX and MDA114, individual-patient outcomes predicted by these two predictors were significantly concordant.

[1146]

**TÍTULO / TITLE:** - Inhibition of the PI3K/AKT-NF-kappaB Pathway With Curcumin Enhanced Radiation-Induced Apoptosis in Human Burkitt's Lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Pharmacol Sci. 2013;121(4):247-56.

**AUTORES / AUTHORS:** - Qiao Q; Jiang Y; Li G

**INSTITUCIÓN / INSTITUTION:** - Department of Radiotherapy, the First Hospital of China Medical University, China.

**RESUMEN / SUMMARY:** - The phosphatidylinositol-3-kinase (PI3K) / protein kinase B (AKT) signal transduction pathway is commonly misregulated in lymphoma and associated with tumorigenesis and enhanced resistance to radiotherapy. Curcumin has been shown to inhibit the PI3K/AKT signal

transduction pathway in several tumor models. In this study, we found that curcumin inhibits constitutive and radiation-induced expression of the PI3K/AKT pathway and its downstream regulator nuclear factor kappaB (NF-kappaB) in human Burkitt's lymphoma, a high-grade non-Hodgkin's lymphoma (NHL). We further demonstrated that the blockage of radiation-induced activation of the PI3K/AKT pathway and its downstream regulator NF-kappaB by either curcumin or specific PI3/AKT inhibitors (LY294002 for PI3K or SH-5 for AKT) enhance apoptosis in three human Burkitt's lymphoma cell lines (Namalwa, Ramos, and Raji) that were treated with ionizing radiation. However, no synergic effect on radiation-induced apoptosis was found in the cells co-pretreated with curcumin combined with LY294002 or curcumin combined with SH-5. The results from this study suggest that curcumin might play an important role in radiotherapy of high-grade NHL through inhibition of the PI3K/AKT-dependent NF-kappaB pathway.

[1147]

**TÍTULO / TITLE:** - Erratum to: Comprehensive overview of the efficacy and safety of sorafenib in advanced or metastatic renal cell carcinoma after a first tyrosine kinase inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Jun;15(6):499. doi: 10.1007/s12094-013-1032-2.

●●Enlace al texto completo (gratis o de pago) [1007/s12094-013-1032-](#)

[2](#)

**AUTORES / AUTHORS:** - Afonso FJ; Anido U; Fernandez-Calvo O; Vazquez-Estevez S; Leon L; Lazaro M; Ramos M; Anton-Aparicio L

**INSTITUCIÓN / INSTITUTION:** - Complejo Hospitalario Arquitecto Marcide, Ferrol, España.

[1148]

**TÍTULO / TITLE:** - Zoledronic acid produces combinatory anti-tumor effects with cisplatin on mesothelioma by increasing p53 expression levels.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e60297. doi: 10.1371/journal.pone.0060297. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060297](#)

**AUTORES / AUTHORS:** - Okamoto S; Jiang Y; Kawamura K; Shingyoji M; Fukamachi T; Tada Y; Takiguchi Y; Tatsumi K; Shimada H; Hiroshima K; Kobayashi H; Tagawa M

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba, Japan.

**RESUMEN / SUMMARY:** - We examined anti-tumor effects of zoledronic acid (ZOL), one of the bisphosphonates agents clinically used for preventing loss of

bone mass, on human mesothelioma cells bearing the wild-type p53 gene. ZOL-treated cells showed activation of caspase-3/7, -8 and -9, and increased sub-G1 phase fractions. A combinatory use of ZOL and cisplatin (CDDP), one of the first-line anti-cancer agents for mesothelioma, synergistically or additively produced the cytotoxicity on mesothelioma cells. Moreover, the combination achieved greater anti-tumor effects on mesothelioma developed in the pleural cavity than administration of either ZOL or CDDP alone. ZOL-treated cells as well as CDDP-treated cells induced p53 phosphorylation at Ser 15, a marker of p53 activation, and up-regulated p53 protein expression levels. Down-regulation of p53 levels with siRNA however did not influence the ZOL-mediated cytotoxicity but negated the combinatory effects by ZOL and CDDP. In addition, ZOL treatments augmented cytotoxicity of adenoviruses expressing the p53 gene on mesothelioma. These data demonstrated that ZOL-mediated augmentation of p53, which was not linked with ZOL-induced cytotoxicity, played a role in the combinatory effects with a p53 up-regulating agent, and suggests a possible clinical use of ZOL to mesothelioma with anti-cancer agents.

[1149]

**TÍTULO / TITLE:** - Tumour necrosis factor alpha, interferon gamma and substance p are novel modulators of extrapituitary prolactin expression in human skin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 23;8(4):e60819. doi: 10.1371/journal.pone.0060819. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060819](http://1371/journal.pone.0060819)

**AUTORES / AUTHORS:** - Langan EA; Vidali S; Pigat N; Funk W; Lisztes E; Biro T; Goffin V; Griffiths CE; Paus R

**INSTITUCIÓN / INSTITUTION:** - Dermatology Research Centre, Manchester Academic Health Science Centre, and Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom ; Department of Dermatology, University of Lubeck, Lubeck, Germany.

**RESUMEN / SUMMARY:** - Human scalp skin and hair follicles (HFs) are extra-pituitary sources of prolactin (PRL). However, the intracutaneous regulation of PRL remains poorly understood. Therefore we investigated whether well-recognized regulators of pituitary PRL expression, which also impact on human skin physiology and pathology, regulate expression of PRL and its receptor (PRLR) in situ. This was studied in serum-free organ cultures of microdissected human scalp HFs and skin, i.e. excluding pituitary, neural and vascular inputs. Prolactin expression was confirmed at the gene and protein level in human truncal skin, where its expression significantly increased ( $p = 0.049$ ) during organ culture. There was, however, no evidence of PRL secretion into the culture medium as measured by ELISA. PRL immunoreactivity (IR) in female

human epidermis was decreased by substance P ( $p = 0.009$ ), while neither the classical pituitary PRL inhibitor, dopamine, nor corticotropin-releasing hormone significantly modulated PRL IR in HFs or skin respectively. Interferon (IFN) gamma increased PRL IR in the epithelium of human HFs ( $p = 0.044$ ) while tumour necrosis factor (TNF) alpha decreased both PRL and PRLR IR. This study identifies substance P, TNFalpha and IFNgamma as novel modulators of PRL and PRLR expression in human skin, and suggests that intracutaneous PRL expression is not under dopaminergic control. Given the importance of PRL in human hair growth regulation and its possible role in the pathogenesis of several common skin diseases, targeting intracutaneous PRL production via these newly identified regulatory pathways may point towards novel therapeutic options for inflammatory dermatoses.

[1150]

**TÍTULO / TITLE:** - Active Component of Danshen (*Salvia miltiorrhiza* Bunge), Tanshinone I, Attenuates Lung Tumorigenesis via Inhibitions of VEGF, Cyclin A, and Cyclin B Expressions.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med.

2013;2013:319247. doi: 10.1155/2013/319247. Epub 2013 Apr 9.

●●Enlace al texto completo (gratis o de pago) [1155/2013/319247](#)

**AUTORES / AUTHORS:** - Tung YT; Chen HL; Lee CY; Chou YC; Lee PY; Tsai HC; Lin YL; Chen CM

**INSTITUCIÓN / INSTITUTION:** - Department of Life Sciences, Agricultural Biotechnology Center, National Chung Hsing University, Taichung 402, Taiwan.

**RESUMEN / SUMMARY:** - Tanshinone I (T1) and tanshinone II (T2) are the major diterpenes isolated from Danshen (*Salvia miltiorrhiza* Bunge). Three human lung adenocarcinoma cell lines, A549, CL1-0, and CL1-5, were treated with T1 and T2 for the in vitro antitumor test. Results showed that T1 was more effective than T2 in inhibiting the growth of lung cancer cells via suppressing the expression of VEGF, Cyclin A, and Cyclin B proteins in a dose-dependent manner. Moreover, a transgenic mice model of the human vascular endothelial growth factor-A165 (hVEGF-A 165) gene-induced pulmonary tumor was further treated with T1 for the in vivo lung cancer therapy test. T1 significantly attenuated hVEGF-A165 overexpression to normal levels of the transgenic mice (Tg) that were pretreated with human monocytic leukemia THP-1 cell-derived conditioned medium (CM). It also suppressed the formation of lung adenocarcinoma tumors (16.7%) compared with two placebo groups (50% for Tg/Placebo and 83.3% for Tg/CM/Placebo;  $P < 0.01$ ). This antitumor effect is likely to slow the progression of cells through the S and G2/M phases of the cell cycle. Blocking of the tumor-activated cell cycle pathway may be a critical mechanism for the observed antitumorigenic effects of T1 treatment on vasculogenesis and angiogenesis.

[1151]

**TÍTULO / TITLE:** - A Systematic Review and Methodological Evaluation of Published Cost-Effectiveness Analyses of Aromatase Inhibitors versus Tamoxifen in Early Stage Breast Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 6;8(5):e62614. doi: 10.1371/journal.pone.0062614. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062614](#)

**AUTORES / AUTHORS:** - John-Baptiste AA; Wu W; Rochon P; Anderson GM; Bell CM

**INSTITUCIÓN / INSTITUTION:** - Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada ; Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada ; Pharmacoeconomics Research Unit, Cancer Care Ontario, Toronto, Ontario, Canada ; Canadian Centre for Applied Research in Cancer Control, Toronto, Ontario, Canada ; Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada.

**RESUMEN / SUMMARY:** - BACKGROUND: A key priority in developing policies for providing affordable cancer care is measuring the value for money of new therapies using cost-effectiveness analyses (CEAs). For CEA to be useful it should focus on relevant outcomes and include thorough investigation of uncertainty. Randomized controlled trials (RCTs) of five years of aromatase inhibitors (AI) versus five years of tamoxifen in the treatment of postmenopausal women with early stage breast cancer, show benefit of AI in terms of disease free survival (DFS) but not overall survival (OS) and indicate higher risk of fracture with AI. Policy-relevant CEA of AI versus tamoxifen should focus on OS and include analysis of uncertainty over key assumptions. METHODS: We conducted a systematic review of published CEAs comparing an AI to tamoxifen. We searched Ovid MEDLINE, EMBASE, PsychINFO, and the Cochrane Database of Systematic Reviews without language restrictions. We selected CEAs with outcomes expressed as cost per life year or cost per quality adjusted life year (QALY). We assessed quality using the Neumann checklist. Using structured forms two abstractors collected descriptive information, sources of data, baseline assumptions on effectiveness and adverse events, and recorded approaches to assessing parameter uncertainty, methodological uncertainty, and structural uncertainty. RESULTS: We identified 1,622 citations and 18 studies met inclusion criteria. All CE estimates assumed a survival benefit for aromatase inhibitors. Twelve studies performed sensitivity analysis on the risk of adverse events and 7 assumed no additional mortality risk with any adverse event. Sub-group analysis was limited; 6 studies examined older women, 2 examined women with low recurrence risk, and 1 examined women with multiple comorbidities. CONCLUSION: Published CEAs comparing AIs to tamoxifen assumed an OS benefit though none has been shown in RCTs,

leading to an overestimate of the cost-effectiveness of AIs. Results of these CEA analyses may be suboptimal for guiding policy.

[1152]

**TÍTULO / TITLE:** - Ubiquitin ligase Cbl-b is involved in icotinib (BPI-2009H)-induced apoptosis and G1 phase arrest of EGFR mutation-positive non-small-cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Res Int. 2013;2013:726375. doi: 10.1155/2013/726375. Epub 2013 Mar 19.

●●Enlace al texto completo (gratis o de pago) [1155/2013/726375](#)

**AUTORES / AUTHORS:** - Mu X; Zhang Y; Qu X; Hou K; Kang J; Hu X; Liu Y

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, The First Hospital of China Medical University, 155 North Nanjing Street, Heping District, Shenyang 110001, China.

**RESUMEN / SUMMARY:** - Epidermal growth factor receptor (EGFR) is one of the most promising targets for non-small-cell lung cancer (NSCLC). Icotinib, a highly selective EGFR tyrosine kinase inhibitor (EGFR-TKI), has shown promising clinical efficacy and safety in patients with NSCLC. The exact molecular mechanism of icotinib remains unclear. In this study, we first investigated the antiproliferative effect of icotinib on NSCLC cells. Icotinib significantly inhibited proliferation of the EGFR-mutated lung cancer HCC827 cells. The IC50 values at 48 and 72 h were 0.67 and 0.07  $\mu$ M, respectively. Flow cytometric analysis showed that icotinib caused the G1 phase arrest and increased the rate of apoptosis in HCC827 cells. The levels of cyclin D1 and cyclin A2 were decreased. The apoptotic process was associated with activation of caspase-3, -8, and poly(ADP-ribose) polymerase (PARP). Further study revealed that icotinib inhibited phosphorylation of EGFR, Akt, and extracellular signal-regulated kinase. In addition, icotinib upregulated ubiquitin ligase Cbl-b expression. These observations suggest that icotinib-induced upregulation of Cbl-b is responsible, at least in part, for the antitumor effect of icotinib via the inhibition of phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase pathways in EGFR-mutated NSCLC cells.

[1153]

**TÍTULO / TITLE:** - Loss of connective tissue growth factor as an unfavorable prognosis factor activates miR-18b by PI3K/AKT/C-Jun and C-Myc and promotes cell growth in nasopharyngeal carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 May 16;4:e634. doi: 10.1038/cddis.2013.153.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.153](#)

**AUTORES / AUTHORS:** - Yu X; Zhen Y; Yang H; Wang H; Zhou Y; Wang E; Marincola FM; Mai C; Chen Y; Wei H; Song Y; Lyu X; Ye Y; Cai L; Wu Q; Zhao M; Hua S; Fu Q; Zhang Y; Yao K; Liu Z; Li X; Fang W

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Cancer Research Institute, Southern Medical University, Guangzhou, PR China.

**RESUMEN / SUMMARY:** - Connective tissue growth factor (CTGF) has different roles in different types of cancer. However, the involvement and molecular basis of CTGF in tumor progression and prognosis of human nasopharyngeal carcinoma (NPC) have almost never been reported. In this study, we observed that downregulated CTGF expression was significantly associated with NPC progression and poor prognosis. Knockdown of CTGF markedly elevated the ability of cell proliferation in vivo and in vitro. Subsequently, we discovered that the reduction of CTGF increased the expression of miR-18b, an oncomir-promoting cell proliferation. Further, we discovered that attenuated CTGF-mediated upregulation of miR-18b was dependent on the increased binding of transcription factors Jun proto-oncogene (C-Jun) and v-Myc myelocytomatosis viral oncogene homolog (C-Myc) to miR-18b promoter region via phosphoinositide 3-kinase (PI3K)/AKT pathway. Finally, we further found that miR-18b directly suppressed the expression of CTGF in NPC. In clinical fresh specimens, miR-18b was widely overexpressed and inversely correlated with CTGF expression in NPC. Our studies are the first to demonstrate that reduced CTGF as an unfavorable prognosis factor mediates the activation of miR-18b, an oncomir directly suppresses CTGF expression, by PI3K/AKT/C-Jun and C-Myc and promotes cell growth of NPC.

[1154]

**TÍTULO / TITLE:** - Pomegranate Bioactive Constituents Suppress Cell Proliferation and Induce Apoptosis in an Experimental Model of Hepatocellular Carcinoma: Role of Wnt/ beta -Catenin Signaling Pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med.

2013;2013:371813. doi: 10.1155/2013/371813. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago) [1155/2013/371813](#)

**AUTORES / AUTHORS:** - Bhatia D; Thoppil RJ; Mandal A; Samtani KA; Darvesh AS; Bishayee A

**INSTITUCIÓN / INSTITUTION:** - Cancer Therapeutics and Chemoprevention Group, Department of Pharmaceutical Sciences, College of Pharmacy, Northeast Ohio Medical University, Rootstown, OH 44272, USA.

**RESUMEN / SUMMARY:** - Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, and chemoprevention represents a viable approach in lowering the mortality of this disease. Pomegranate fruit, an abundant source of anti-inflammatory phytochemicals, is gaining tremendous attention for its wide-spectrum health benefits. We previously reported that a characterized pomegranate emulsion (PE) prevents diethylnitrosamine (DENA)-

induced rat hepatocarcinogenesis through inhibition of nuclear factor-kappaB (NF- kappa B). Since NF- kappa B concurrently induces Wnt/ beta -catenin signaling implicated in cell proliferation, cell survival, and apoptosis evasion, we examined antiproliferative, apoptosis-inducing and Wnt/ beta -catenin signaling-modulatory mechanisms of PE during DENA rat hepatocarcinogenesis. PE (1 or 10 g/kg) was administered 4 weeks before and 18 weeks following DENA exposure. There was a significant increase in hepatic proliferation (proliferating cell nuclear antigen) and alteration in cell cycle progression (cyclin D1) due to DENA treatment, and PE dose dependently reversed these effects. PE substantially induced apoptosis by upregulating proapoptotic protein Bax and downregulating antiapoptotic protein Bcl-2. PE dose dependently reduced hepatic beta -catenin and augmented glycogen synthase kinase-3 beta expression. Our study provides evidence that pomegranate phytochemicals exert chemoprevention of hepatic cancer through antiproliferative and proapoptotic mechanisms by modulating Wnt/ beta -catenin signaling. PE, thus, targets two interconnected molecular circuits (canonical NF- kappa B and Wnt/ beta -catenin pathways) to exert chemoprevention of HCC.

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[1155]

**TÍTULO / TITLE:** - Prognostic value of different patterns of squamous cell carcinoma antigen level for the recurrent cervical cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Res. Acceso gratuito al texto completo a partir de 1 año de la fecha de publicación.

●●Enlace a la Editora de la Revista <http://cancerres.aacrjournals.org/>

●●Cita: Cancer Research: <> Treat. 2013 Mar;45(1):48-54. doi: 10.4143/crt.2013.45.1.48. Epub 2013 Mar 31.

●●Enlace al texto completo (gratuito o de pago) [4143/crt.2013.45.1.48](#)

**AUTORES / AUTHORS:** - Jeong BK; Huh SJ; Choi DH; Park W; Bae DS; Kim BG

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. ; Department of Radiation Oncology, Gyeongsang National University School of Medicine, Jinju, Korea. ; Institute of Health Science, Gyeongsang National University, Jinju, Korea.

**RESUMEN / SUMMARY:** - PURPOSE: In some unusual cases, in patients with cervical cancer, an elevation of squamous cell carcinoma antigen (SCC-Ag) was not observed at diagnosis but was observed on recurrence, or vice versa. The objective of this study was to identify patient-, disease-, and treatment-related factors associated with this unusual level of SCC-Ag, and to determine whether SCC-Ag is a useful tumor marker in such patients. MATERIALS AND METHODS: Among 129 patients with recurrence, 14 who showed a normal SCC-Ag level at diagnosis but an elevated level at recurrence were classified as group I; 22 patients with an elevated SCC-Ag level at diagnosis but not at recurrence were classified as group II; and 76 patients with an elevated SCC-

Ag level at both diagnosis and recurrence were classified as group III. RESULTS: In univariate analysis, unusual SCC-Ag showed statistically significant relationships with pathology and biochemical response to treatment. However, in the multivariate analysis, none of the clinicopathologic factors showed a statistical relationship with unusual levels of SCC-Ag. The 5-year disease-free survival rates for groups I, II, and III were 7.1%, 9.1%, and 0% (p=0.418), and the 5-year overall survival rates were 34.3%, 58.4%, and 33.3% (p=0.142), respectively. CONCLUSION: The value of SCC-Ag has been confirmed in all patients; thus, check of SCC-Ag level at follow-up should be considered. Although no statistically significant differences were observed among the groups, we conclude that patients with a high initial SCC-Ag and elevated SCC-Ag at relapse have poor prognosis due to high SCC-Ag level.

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[1156]

**TÍTULO / TITLE:** - Activity of angiogenesis inhibitors in metastatic epithelioid hemangioendothelioma: a case report.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Med. 2012 Jun;9(2):133-6. doi: 10.3969/j.issn.2095-3941.2012.02.010.

●●Enlace al texto completo (gratis o de pago) [3969/j.issn.2095-3941.2012.02.010](#)

**AUTORES / AUTHORS:** - Gaur S; Torabi A; O'Neill TJ

**INSTITUCIÓN / INSTITUTION:** - Divisions of Hematology-Oncology, Texas Tech University Health Science Center, TX 79905, USA.

**RESUMEN / SUMMARY:** - This report describes a patient with metastatic epithelioid hemangioendothelioma treated with bevacizumab and nanoparticle albumin-bound paclitaxel. The treatment was well tolerated and led to the stabilization of an aggressive variant of the disease. This case report is the first one that describes the activity of the combination of chemotherapy and bevacizumab in epithelioid hemangioendothelioma. Literature describing the activity of bevacizumab and other agents (thalidomide, lenalidomide, and interferon) believed to possess anti-angiogenic activities is also reviewed.

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[1157]

**TÍTULO / TITLE:** - Curability of Poor-Risk Metastatic Sarcomatoid Renal Cell Carcinoma with the Combination of Gemcitabine, 5-Fluorouracil, and Interferon-Alfa: A Case Report of a 55-Year-Old Man with a 10-Year Complete Remission.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Genitourin Cancer. 2013 May 9. pii: S1558-7673(13)00051-7. doi: 10.1016/j.clgc.2013.04.005.

●●Enlace al texto completo (gratis o de pago) [1016/j.clgc.2013.04.005](#)

**AUTORES / AUTHORS:** - Conter HJ; Lim ZD; Ng CS; Millikan RE; Tannir NM

**INSTITUCIÓN / INSTITUTION:** - Division of Cancer Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX. Electronic address: [hjconter@mdanderson.org](mailto:hjconter@mdanderson.org).

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[1158]

**TÍTULO / TITLE:** - Determination of the optimal tubulin isotype target as a method for the development of individualized cancer chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Theor Biol Med Model. 2013 May 1;10:29. doi: 10.1186/1742-4682-10-29.

●●Enlace al texto completo (gratis o de pago) [1186/1742-4682-10-29](#)

**AUTORES / AUTHORS:** - Ravanbakhsh S; Gajewski M; Greiner R; Tuszynski JA

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, University of Alberta, Edmonton, AB T6G 1Z2, Canada. [jackt@ualberta.ca](mailto:jackt@ualberta.ca).

**RESUMEN / SUMMARY:** - BACKGROUND: As microtubules are essential for cell growth and division, its constituent protein beta-tubulin has been a popular target for various treatments, including cancer chemotherapy. There are several isotypes of human beta-tubulin and each type of cell expresses its characteristic distribution of these isotypes. Moreover, each tubulin-binding drug has its own distribution of binding affinities over the various isotypes, which further complicates identifying the optimal drug selection. An ideal drug would preferentially bind only the tubulin isotypes expressed abundantly by the cancer cells, but not those in the healthy cells. Unfortunately, as the distributions of the tubulin isotypes in cancer cells overlap with those of healthy cells, this ideal scenario is clearly not possible. We can, however, seek a drug that interferes significantly with the isotype distribution of the cancer cell, but has only minor interactions with those of the healthy cells. METHODS: We describe a quantitative methodology for identifying this optimal tubulin isotype profile for an ideal cancer drug, given the isotype distribution of a specific cancer type, as well as the isotype distributions in various healthy tissues, and the physiological importance of each such tissue. RESULTS: We report the optimal isotype profiles for different types of cancer with various routes of delivery. CONCLUSIONS: Our algorithm, which defines the best profile for each type of cancer (given the drug delivery route and some specified patient characteristics), will help to personalize the design of pharmaceuticals for individual patients. This paper is an attempt to explicitly consider the effects of the tubulin isotype distributions in both cancer and normal cell types, for rational chemotherapy design aimed at optimizing the drug's efficacy with minimal side effects.

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[1159]

**TÍTULO / TITLE:** - Metastatic renal cell carcinoma: how to make the best sequencing decision after withdrawal for intolerance to a tyrosine kinase inhibitor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 Jun;9(6):831-43. doi: 10.2217/fon.13.58.

●●Enlace al texto completo (gratis o de pago) [2217/fon.13.58](#)

**AUTORES / AUTHORS:** - Sabbatini R; Ortega C; Procopio G; Masini C; Galligioni E; Porta C

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology & Haematology & Respiratory Disease, University Hospital, Modena, Italy.

**RESUMEN / SUMMARY:** - With seven agents approved for metastatic renal cell carcinoma (RCC) within the past few years, there has undoubtedly been progress in treating this disease. The treatment safety of these new agents, however, now represents a crucial concern, which requires a search for the best possible balance between the minimization of the treatment burden and the need for maintaining appropriate drug dosages able to induce the best clinical benefit. In this review we have analyzed safety data of all approved targeted agents for metastatic RCC available as first- or second-line therapy to provide suggestions aimed at establishing the most appropriate second-line or later treatment on the basis of toxicities that have arisen in therapy. Based on the characteristics and comorbidities of the patients and on the toxicity profile of each treatment, it is possible to plan different therapeutic options. We, therefore, have compiled a list of points that are important to keep in mind when considering the use of the targeted drugs for the treatment of advanced RCC.

[1160]

**TÍTULO / TITLE:** - In silico prediction of 3D structure of Mn superoxide dismutase of *Scylla serrata* and its binding properties with inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Interdiscip Sci. 2013 Mar;5(1):69-76. doi: 10.1007/s12539-013-0150-4. Epub 2013 Apr 19.

●●Enlace al texto completo (gratis o de pago) [1007/s12539-013-0150-](#)

[4](#)

**AUTORES / AUTHORS:** - Paital B; Kumar S; Farmer R; Chainy GB

**INSTITUCIÓN / INSTITUTION:** - Department of Zoology, Utkal University, Bhubaneswar 751004, India.

**RESUMEN / SUMMARY:** - In the present study, we used computational methods to model crab and rat MnSOD using the crystal structure of MnSOD from *Homo sapiens* (PDB code: 1MSD) as template by comparative modeling approach. We performed molecular dynamics simulations to study dynamic behavior of the crab MnSOD. The modeled proteins were validated and subjected to molecular docking analyses. Molecular docking tool was used to elucidate a comparative binding mode of the crab and rat SOD with potent inhibitors of SOD such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), potassium cyanide (KCN) and sodium dodecyl sulphate (SDS). The predicted valid structure of crab MnSOD did not show any interaction with KCN but close interaction with H<sub>2</sub>O<sub>2</sub> and SDS. A possible

inhibitory mechanism of SDS and H<sub>2</sub>O<sub>2</sub> due to their interaction with the amino acids present in the active site of the MnSOD of the above two animals are elucidated. This allowed us to predict the binding modes of the proteins to elucidate probable mode of action and sites of interference.

[1161]

**TÍTULO / TITLE:** - A combination of cytokines rescues highly purified leukemic CLL B-cells from spontaneous apoptosis in vitro.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(3):e60370. doi: 10.1371/journal.pone.0060370. Epub 2013 Mar 26.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060370](#)

**AUTORES / AUTHORS:** - Ghamlouch H; Ouled-Haddou H; Damaj G; Royer B; Gubler B; Marolleau JP

**INSTITUCIÓN / INSTITUTION:** - EA4666, Laboratoire d'Immunologie, Université de Picardie Jules Verne, UFR de Médecine, Amiens, France.

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**RESUMEN / SUMMARY:** - B-chronic lymphocytic leukemia (B-CLL), the most common human leukemia, is characterized by predominantly non-dividing malignant mature CD5+ B lymphocytes with an apoptosis defect. Various microenvironmental stimuli confer a growth advantage on these leukemic cells and extend their survival in vivo. Nevertheless, when cultured in vitro, CLL B-cells rapidly die from apoptosis. Certain cytokines may extend the survival capacity of CLL B-cells in vitro and individual anti-apoptotic effects of several cytokines have been reported. The potential cumulative effect of such cytokines has not been studied. We therefore investigated the effects on CLL B-cells survival in vitro of humoral factors, polyclonal lymphocyte activators and a combination of cytokines known for their anti-apoptotic effects. Purified CLL B-cells were cultured in the presence or absence of various soluble molecules and the leukemic cell response was assessed in terms of viability. Apoptotic cell death was detected by flow cytometry using annexinV and 7-amino-actinomycin. The survival of CLL B-cells in vitro was highly variable. When tested separately, cytokines (IL-2, -6, -10, -12, -15, -21, BAFF and APRIL) improved CLL B cell survival moderately; in combination, they significantly enhanced survival of these cells, even up to 7 days of culture. We also report that humoral factors from autologous serum are important for survival of these malignant cells. Our findings support the concept that the CLL microenvironment is critical and suggest that soluble factors may contribute directly to the prolonged survival of CLL B-cells. Therefore, the combination of cytokines we describe as providing strong resistance to apoptosis in vitro might be used to improve the treatment of CLL.

[1162]

**TÍTULO / TITLE:** - KAI1/CD82 and CyclinD1 as biomarkers of invasion, metastasis and prognosis of laryngeal squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Exp Pathol. 2013 May 15;6(6):1060-7. Print 2013.

**AUTORES / AUTHORS:** - Zhang B; Liu W; Li L; Lu J; Liu M; Sun Y; Jin D

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology/Head and Neck Surgery, Second Affiliated Hospital of Harbin Medical University Harbin, 150081, P. R. China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** This study aimed to investigate the expressions and significance of KAI1/CD82 and CyclinD1 in laryngeal squamous cell carcinoma (LSCC). **METHODS:** Real-time quantitative PCR (Q-PCR) and Western blot assay were employed to detect the expressions of KAI1/CD82 and CyclinD1 in the laryngeal tissues of 86 LSCC patients, 32 patients with laryngeal polyp and 38 patients with laryngeal leukoplakia, and the influence of both proteins on the clinicopathological features and survival of LSCC patients. **RESULTS:** The changes in mRNA and protein expressions of KAI1/CD82 and CyclinD1 were consistent in three groups, and the expressions of KAI1/CD82 and CyclinD1 were significantly different among three groups ( $P < 0.01$  or  $< 0.05$ ). The KAI1/CD82 expression in patients with TNM stage III-IV LSCC, poorly differentiated LSCC, clinical stage III-IV LSCC or lymph node metastasis was markedly lower than that in those with TNM stage I-II LSCC, well differentiated LSCC, clinical stage I-II LSCC or no lymph node metastasis ( $P < 0.01$  or  $< 0.05$ ). However, there was no marked difference in KAI1/CD82 expression between males and females and among patients in different age groups ( $P > 0.05$ ). In LSCC patients positive for KAI1/CD82 protein expression, the median survival time was 76 months, which was significantly longer than that in LSCC patients negative for KAI1/CD82 protein expression (48 months;  $X(2) = 16.293$ ,  $P = 0.000$ ). The CyclinD1 expression in patients with TNM stage III-IV LSCC, poorly differentiated LSCC, or clinical stage III-IV LSCC was dramatically higher than that in patients with TNM stage I-II LSCC, well differentiated LSCC, or clinical stage I-II LSCC ( $P < 0.01$  or  $< 0.05$ ). However, no marked difference was noted in CyclinD1 expression between males and females, among patients in different age groups and between patients with and without lymph node metastasis ( $P > 0.05$ ). In LSCC patients positive for CyclinD1 protein expression, the median survival time was 40 months, which was markedly shorter than that in LSCC patients negative for CyclinD1 protein expression ( $X(2) = 9.517$ ,  $P = 0.02$ ). In LSCC patients, there was a negative correlation between KAI1/CD82 expression and CyclinD1 expression ( $X(2) = 7.86$ ,  $P < 0.01$ ). **CONCLUSION:** KAI1/CD82 affects cell cycle. Both KAI1/CD82 and CyclinD1 are involved in the occurrence and development of LSCC, and may provide clinical information for evaluation of invasiveness, metastasis and prognosis of LSCC. Thus, KAI1/CD82 and CyclinD1 may serve

as markers for determination of invasiveness, metastasis and prognosis of LSCC.

[1163]

**TÍTULO / TITLE:** - Cyclin D1 overexpression is associated with poor prognosis in oropharyngeal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Otolaryngol Head Neck Surg. 2013 Mar 19;42(1):23. doi: 10.1186/1916-0216-42-23.

●●Enlace al texto completo (gratis o de pago) [1186/1916-0216-42-23](#)

**AUTORES / AUTHORS:** - Lin RJ; Lubpairee T; Liu KY; Anderson DW; Durham S; Poh CF

**INSTITUCIÓN / INSTITUTION:** - Integrative Oncology, BC Cancer Agency & Research Centre, Vancouver, BC, Canada. [CPoh@bccancer.bc.ca](mailto:CPoh@bccancer.bc.ca).

**RESUMEN / SUMMARY:** - OBJECTIVES: To determine the biological characteristics of oropharyngeal squamous cell carcinoma (OpSCC) and related outcome. DESIGN: Retrospective study. METHODS: Patients (N=60) with primary OpSCC from 2000 to 2005 were retrospectively identified from Pathology database and the outcome was confirmed through chart review. Among these, 41 biopsy samples with enough tissues were retrieved to construct a tissue microarray for detection of the presence of high-risk human papillomavirus (HPV) using Chromogenic in situ hybridization (CISH) as well as the expression of p16 and cyclin D1 using immunohistochemistry. MAIN OUTCOME MEASURES: Disease-free survival. RESULTS: Among 60 patients, 39 (65%) patients had no recurrence or died without disease at the last follow-up (disease-free survival or Group 1), and 21 (35%) patients had persistent disease or died of disease (progression-free survival or Group 2). Although follow-up time was twice as long in group 1 (4.7 +/- 2.2 vs. 2.0 +/- 1.6 years; P < 0.0001), there was no difference between the 2 groups in age, gender, smoking/alcohol habits, TNM staging and treatment modalities. Among those 41 cases with available tumour tissues, there was no difference in HPV status and p16 expression between the 2 groups but a significant difference in cyclin D1 expression (P = 0.05). Using Kaplan-Meier survival analysis and log-rank test, cyclin D1 overexpression was highly associated with a poor prognosis when comparing time to outcome (P < 0.0001). CONCLUSION: Cyclin D1 overexpression is a potential prognostic marker of OpSCC.

[1164]

**TÍTULO / TITLE:** - Prognostic significance of ploidy and S-phase fraction in primary intraoral squamous cell carcinoma and their corresponding metastatic lymph nodes.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Egypt Natl Canc Inst. 2012 Mar;24(1):7-14. doi: 10.1016/j.jnci.2011.12.001. Epub 2012 Jan 10.

●●Enlace al texto completo (gratis o de pago) [1016/j.inci.2011.12.001](https://doi.org/10.1016/j.inci.2011.12.001)

**AUTORES / AUTHORS:** - El-Deftar MF; El Gerzawi SM; Abdel-Azim AA; Tohamy SM

**INSTITUCIÓN / INSTITUTION:** - The Department of Pathology, National Cancer Institute, Cairo University, Egypt. [eldefarmerv@yahoo.com](mailto:eldefarmerv@yahoo.com)

**RESUMEN / SUMMARY:** - BACKGROUND: Despite improvements in diagnosis and therapy of oral and oro-pharyngeal carcinomas during the past 30 years the 5-year disease-free survival is still poor. Patient's prognosis is affected by cervical lymph node metastasis rather than primary tumors. The DNA ploidy and S-phase fraction (SPF) are associated with tumor aggressiveness and patient outcome in many solid tumors. PURPOSE: Analysis of DNA ploidy and SPF in primary oral squamous cell carcinoma (OSCC) and corresponding node metastasis as prognostic markers in relation to conventional prognostic factors and disease-free survival (DFS). METHODS: Ploidy status and SPF (mean value) of 37 formalin-fixed paraffin embedded (FFPE) primary OSCC tumors and their corresponding lymph node metastasis were assessed by flow cytometry (FCM) and correlated with clinicopathologic prognostic parameters and DFS. RESULTS: Most of OSCC tumors (86.5%) were Grade II. Among primary OSCC the incidence of aneuploidy was 19%, 51.4% showed high SPF (>10.62%) and 48.6% had low SPF (<10.62%). Border line significance (P=0.10) was detected between ploidy status and SPF in primary tumors. In lymph node metastases all tumors were diploid, 78.4% of metastatic tumors revealed low SPF and only 21.6% showed high SPF. There was a statistically significant correlation ( $p=0.02$ ) between site of tumors and DFS and a highly statistically significant correlation ( $p=0.01$ ) between SPF of primary tumors and DFS. CONCLUSIONS: High SPF of primary OSCC tumors assessed by FCM was significantly associated with decreased disease free survival rates. DNA ploidy showed no relationship to bad prognostic indicators in either primary OSCC or their metastatic tumors.

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[1165]

**TÍTULO / TITLE:** - Genomic, prognostic, and cell-signaling advances in uveal melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am Soc Clin Oncol Educ Book. 2013;2013:388-91. doi: E10.1200/EdBook\_AM.2013.33.388.

●●Enlace al texto completo (gratis o de pago)

[1200/EdBook\\_AM.2013.33.388](https://doi.org/10.1200/EdBook_AM.2013.33.388)

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**INSTITUCIÓN / INSTITUTION:** - From the Ocular Oncology Service, Bascom Palmer Eye Institute and Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL.

**RESUMEN / SUMMARY:** - Uveal melanoma (UM) is the second-most common form of melanoma and the most common primary intraocular malignancy. Up to

one-half of patients are at risk for fatal metastatic disease. The metastatic potential of an individual tumor can be accurately determined by analysis of a fine-needle aspirate with gene expression profiling assay that is available for routine clinical use through a commercial Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. The test renders one of two results-class 1 (low metastatic risk) or class 2 (high metastatic risk)-and has been extensively validated in multiple centers. Until recently, the genetic mutations and signaling aberrations in UM were largely unknown. With the advent of new genomic sequencing technologies, however, the molecular landscape of UM is rapidly emerging. Mutations in the Gq alpha subunits GNAQ and GNA11 are mutually exclusive and represent early or initiating events that constitutively activate the MAPK pathway. Mutations in BRCA1-associated protein-1 (BAP1) and splicing factor 3B subunit 1 (SF3B1) also appear to be largely mutually exclusive, and they occur later in tumor progression. BAP1 mutations are strongly associated with metastasis, whereas SF3B1 mutations are associated with a more favorable outcome. BAP1 mutations can arise in the germ line, leading to a newly described BAP1 familial cancer syndrome. These discoveries have led to new clinical trials to assess several classes of compounds, including MEK, protein kinase C, and histone deacetylase inhibitors, in the adjuvant setting for high-risk patients identified as class 2, as well as in the setting of advanced disseminated disease.

[1166]

**TÍTULO / TITLE:** - MACC1 as a Prognostic Biomarker for Early-Stage and AFP-Normal Hepatocellular Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 23;8(5):e64235. doi: 10.1371/journal.pone.0064235. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064235](http://1371/journal.pone.0064235)

**AUTORES / AUTHORS:** - Xie C; Wu J; Yun J; Lai J; Yuan Y; Gao Z; Li M; Li J; Song L

**INSTITUCIÓN / INSTITUTION:** - Department of Infectious Diseases, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China ; State Key Laboratory of Oncology in Southern China, Department of Experimental Research, Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong Province, China.

**RESUMEN / SUMMARY:** - BACKGROUND: The metastasis-associated in colon cancer 1 gene (MACC1) has been found to be associated with cancer development and progression. The aim of this study was to investigate the prognostic value of MACC1 in early-stage and AFP-normal hepatocellular carcinoma (HCC). METHODS: mRNA and protein levels of MACC1 expression in one normal liver epithelial cells THLE3 and 15 HCC cell lines were examined using reverse transcription-PCR and Western blot. MACC1 expression was

also comparatively studied in 6 paired HCC lesions and the adjacent non-cancerous tissue samples. Immunohistochemistry was employed to analyze MACC1 expression in 308 clinicopathologically characterized HCC cases. Statistical analyses were applied to derive association between MACC1 expression scores and clinical staging as well as patient survival. RESULTS: Levels of MACC1 mRNA and protein were higher in HCC cell lines and HCC lesions than in normal liver epithelial cells and the paired adjacent noncancerous tissues. Significant difference in MACC1 expression was found in patients of different TNM stages ( $P < 0.001$ ). Overall survival analysis showed that high MACC1 expression level correlated with lower survival rate ( $P = 0.001$ ). Importantly, an inverse correlation between MACC1 level and patient survival remained significant in subjects with early-stage HCC or with normal serum AFP level. CONCLUSIONS: MACC1 protein may represent a promising biomarker for predicting the prognosis of HCC, including in early-stage and AFP-normal patients.

[1167]

**TÍTULO / TITLE:** - Prognostic relevance of cytochrome C oxidase in primary glioblastoma multiforme.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 10;8(4):e61035. doi: 10.1371/journal.pone.0061035. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061035](#)

**AUTORES / AUTHORS:** - Griguer CE; Cantor AB; Fathallah-Shaykh HM; Gillespie GY; Gordon AS; Markert JM; Radovanovic I; Clement-Schatlo V; Shannon CN; Oliva CR

**INSTITUCIÓN / INSTITUTION:** - Division of Neurosurgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, United States of America. [cgriguer@uab.edu](mailto:cgriguer@uab.edu)

**RESUMEN / SUMMARY:** - Patients with primary glioblastoma multiforme (GBM) have one of the lowest overall survival rates among cancer patients, and reliable biomarkers are necessary to predict patient outcome. Cytochrome c oxidase (CcO) promotes the switch from glycolytic to OXPHOS metabolism, and increased CcO activity in tumors has been associated with tumor progression after chemotherapy failure. Thus, we investigated the relationship between tumor CcO activity and the survival of patients diagnosed with primary GBM. A total of 84 patients with grade IV glioma were evaluated in this retrospective cohort study. Cumulative survival was calculated by the Kaplan-Meier method and analyzed by the log-rank test, and univariate and multivariate analyses were performed with the Cox regression model. Mitochondrial CcO activity was determined by spectrophotometrically measuring the oxidation of cytochrome c. High CcO activity was detected in a subset of glioma tumors (approximately 30%), and was an independent prognostic factor for shorter

progression-free survival and overall survival [P = 0.0087 by the log-rank test, hazard ratio = 3.57 for progression-free survival; P<0.001 by the log-rank test, hazard ratio = 10.75 for overall survival]. The median survival time for patients with low tumor CcO activity was 14.3 months, compared with 6.3 months for patients with high tumor CcO activity. High CcO activity occurs in a significant subset of high-grade glioma patients and is an independent predictor of poor outcome. Thus, CcO activity may serve as a useful molecular marker for the categorization and targeted therapy of GBMs.

[1168]

**TÍTULO / TITLE:** - Association of the epithelial-to-mesenchymal transition phenotype with responsiveness to the p21-activated kinase inhibitor, PF-3758309, in colon cancer models.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Front Pharmacol. 2013;4:35. doi: 10.3389/fphar.2013.00035. Epub 2013 Mar 28.

●●Enlace al texto completo (gratis o de pago) [3389/fphar.2013.00035](#)

**AUTORES / AUTHORS:** - Pitts TM; Kulikowski GN; Tan AC; Murray BW; Arcaroli JJ; Tentler JJ; Spreafico A; Selby HM; Kachaeva MI; McPhillips KL; Britt BC; Bradshaw-Pierce EL; Messersmith WA; Varella-Garcia M; Eckhardt SG

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, University of Colorado Anschutz Medical Campus Aurora, CO, USA.

**RESUMEN / SUMMARY:** - The p21-activated kinase (PAK) family of serine/threonine kinases, which are overexpressed in several cancer types, are critical mediators of cell survival, motility, mitosis, transcription, and translation. In the study presented here, we utilized a panel of colorectal cancer (CRC) cell lines to identify potential biomarkers of sensitivity or resistance that may be used to individualize therapy to the PAK inhibitor PF-03758309. We observed a wide range of proliferative responses in the CRC cell lines exposed to PF-03758309, this response was recapitulated in other phenotypic assays such as anchorage-independent growth, three-dimensional (3D) tumor spheroid formation, and migration. Interestingly, we observed that cells most sensitive to PF-03758309 exhibited up-regulation of genes associated with a mesenchymal phenotype (CALD1, VIM, ZEB1) and cells more resistant had an up-regulation of genes associated with an epithelial phenotype (CLDN2, CDH1, CLDN3, CDH17) allowing us to derive an epithelial-to-mesenchymal transition (EMT) gene signature for this agent. We assessed the functional role of EMT-associated genes in mediating responsiveness to PF-3758309, by targeting known genes and transcriptional regulators of EMT. We observed that suppression of genes associated with the mesenchymal phenotype conferred resistance to PF-3758309, in vitro and in vivo. These results indicate that PAK inhibition is associated with a unique response phenotype in CRC and that further studies should be conducted to facilitate both patient selection and rational combination strategies with these agents.

[1169]

**TÍTULO / TITLE:** - A Phosphoproteomics Approach to Identify Candidate Kinase Inhibitor Pathway Targets in Lymphoma-Like Primary Cell Lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Drug Discov Technol. 2013 May 20.

**AUTORES / AUTHORS:** - Vojvodic M; Hansford LM; Morozova O; Blakely KM; Taylor P; Fathers KE; Moffat J; Marra M; Smith KM; Moran MF; Kaplan DR

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Genetics, University of Toronto, Toronto, Ontario, M5S 1A8, Canada.

**RESUMEN / SUMMARY:** - Mass spectrometry-based technologies are increasingly utilized in drug discovery. Phosphoproteomics in particular has allowed for the efficient surveying of phosphotyrosine signaling pathways involved in various diseases states, most prominently in cancer. We describe a phosphotyrosine-based proteomics screening approach to identify signaling pathways and tyrosine kinase inhibitor targets in highly tumorigenic human lymphoma-like primary cells. We identified several receptor tyrosine kinase pathways and validated SRC family kinases (SFKs) as potential drug targets for targeted selection of small molecule inhibitors. BMS-354825 (dasatinib) and SKI-606 (bosutinib), second and third generation clinical SFK/ABL inhibitors, were found to be potent cytotoxic agents against tumorigenic cells with low toxicity to normal pediatric stem cells. Both SFK inhibitors reduced ERK1/2 and AKT phosphorylation and induced apoptosis. This study supports the adaptation of high-end mass spectrometry techniques for the efficient identification of candidate tyrosine kinases as novel therapeutic targets in primary cancer cell lines.

[1170]

**TÍTULO / TITLE:** - Polo-like kinase 1 inhibitors, mitotic stress and the tumor suppressor p53.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Cycle. 2013 May 1;12(9):1340-51. doi: 10.4161/cc.24573. Epub 2013 Apr 10.

●●Enlace al texto completo (gratis o de pago) [4161/cc.24573](#)

**AUTORES / AUTHORS:** - Sanhaji M; Louwen F; Zimmer B; Kreis NN; Roth S; Yuan J

**INSTITUCIÓN / INSTITUTION:** - Department of Gynecology and Obstetrics; School of Medicine; J.W. Goethe-University; Frankfurt, Germany.

**RESUMEN / SUMMARY:** - Polo-like kinase 1 has been established as one of the most attractive targets for molecular cancer therapy. In fact, multiple small-molecule inhibitors targeting this kinase have been developed and intensively investigated. Recently, it has been reported that the cytotoxicity induced by Plk1 inhibition is elevated in cancer cells with inactive p53, leading to the hypothesis that inactive p53 is a predictive marker for the response of Plk1 inhibition. In

our previous study based on different cancer cell lines, we showed that cancer cells with wild type p53 were more sensitive to Plk1 inhibition by inducing more apoptosis, compared with cancer cells depleted of p53. In the present work, we further demonstrate that in the presence of mitotic stress induced by different agents, Plk1 inhibitors strongly induced apoptosis in HCT116 p53 (+/+) cells, whereas HCT116 p53 (-/-) cells arrested in mitosis with less apoptosis. Depletion of p53 in HCT116 p53 (+/+) or U2OS cells reduced the induction of apoptosis. Moreover, the surviving HCT116 p53 (-/-) cells showed DNA damage and a strong capability of colony formation. Plk1 inhibition in combination with other anti-mitotic agents inhibited proliferation of tumor cells more strongly than Plk1 inhibition alone. Taken together, the data underscore that functional p53 strengthens the efficacy of Plk1 inhibition alone or in combination by strongly activating cell death signaling pathways. Further studies are required to investigate if the long-term outcomes of losing p53, such as low differential grade of tumor cells or defective DNA damage checkpoint, are responsible for the cytotoxicity of Plk1 inhibition.

[1171]

**TÍTULO / TITLE:** - Characterization of the Inhibitor of KappaB Kinase (IKK) Complex in Granulosa Cell Tumors of the Ovary and Granulosa Cell Tumor-Derived Cell Lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Horm Cancer. 2013 May 15.

●●Enlace al texto completo (gratis o de pago) [1007/s12672-013-0146-](#)

[X](#)

**AUTORES / AUTHORS:** - Jamieson S; Fuller PJ

**INSTITUCIÓN / INSTITUTION:** - Steroid Receptor Biology Laboratory, Prince Henry's Institute of Medical Research, Melbourne, VIC, 3168, Australia.

**RESUMEN / SUMMARY:** - Granulosa cell tumors of the ovary (GCT) are a distinct, hormonally active subset of ovarian cancers. Although it has recently been shown that approximately 97 % of all adult GCT harbor a novel somatic missense mutation in the FOXL2 gene, given its almost universal presence, it does not explain differences in tumor stage and/or recurrence. The nuclear factor kappaB (NFkappaB) transcription factor is constitutively active in two human GCT-derived cell lines, COV434 and KGN, which are useful in vitro models to investigate juvenile and adult GCT, respectively. This study aimed to determine the molecular basis and pathogenetic significance of this aberrant NFkappaB activity. Selective chemical inhibitors were used to target candidate components of the pathway. The constitutive activity was blocked by two independent inhibitors of IkappaBalpha phosphorylation, suggesting that aberrant activation occurs upstream of this point. NFkappaB inhibition resulted in a dose-dependent decrease in cell proliferation and viability and a dose-dependent increase in apoptosis. Inhibitors of earlier components of the pathway were without effect. Two independent inhibitors of inhibitor of kappaB

kinase (IKK)beta, a catalytic subunit of the NFkappaB activation complex, were unable to inhibit the constitutive activity, but surprisingly also ligand-induced activity. These findings suggest a central role for IKKbeta; however, no mutations or altered expression of the IKKbeta, IKKalpha, or IKKgamma genes was observed in the cell lines or in a panel of human GCT samples. This study highlights unresolved issues in understanding the pathogenesis of GCT and in the use of the COV434 and KGN cells lines as model systems.

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[1172]

**TÍTULO / TITLE:** - ABT-263 Enhances Sensitivity to Metformin and 2-Deoxyglucose in Pediatric Glioma by Promoting Apoptotic Cell Death.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 17;8(5):e64051. doi: 10.1371/journal.pone.0064051. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0064051](http://1371/journal.pone.0064051)

**AUTORES / AUTHORS:** - Levesley J; Steele L; Taylor C; Sinha P; Lawler SE

**INSTITUCIÓN / INSTITUTION:** - Translational Neuro-Oncology Group, Leeds Institute of Molecular Medicine, University of Leeds, St James's University Hospital, Leeds, United Kingdom.

**RESUMEN / SUMMARY:** - Pediatric high grade glioma is refractory to conventional multimodal treatment, highlighting a need to develop novel efficacious therapies. We investigated tumor metabolism as a potential therapeutic target in a panel of diverse pediatric glioma cell lines (SF188, KNS42, UW479 and RES186) using metformin and 2-deoxyglucose. As a single agent, metformin had little effect on cell viability overall. SF188 cells were highly sensitive to 2-deoxyglucose however, combination of metformin with 2-deoxyglucose significantly reduced cell proliferation compared to either drug alone in all cell lines tested. In addition, the combination of the two agents was associated with a rapid decrease in cellular ATP and subsequent AMPK activation. However, increased cell death was only observed in select cell lines after prolonged exposure to the drug combination and was caspase independent. Anti-apoptotic BCL-2 family proteins have been indicated as mediators of resistance against metabolic stress. Therefore we sought to determine whether pharmacological inhibition of BCL-2/BCL-xL with ABT-263 could potentiate apoptosis in response to these agents. We found that ABT-263 increased sensitivity to 2-deoxyglucose and promoted rapid and extensive cell death in response to the combination of 2-deoxyglucose and metformin. Furthermore, cell death was inhibited by the pan-caspase inhibitor, z-VAD-FMK suggesting that ABT-263 potentiated caspase-dependent cell death in response to 2-deoxyglucose or its combination with metformin. Overall, these data provide support for the concept that targeting metabolic and anti-apoptotic pathways may be an effective therapeutic strategy in pediatric glioma.

[1173]

**TÍTULO / TITLE:** - Phyllanthus Suppresses Prostate Cancer Cell, PC-3, Proliferation and Induces Apoptosis through Multiple Signalling Pathways (MAPKs, PI3K/Akt, NFkappaB, and Hypoxia).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:609581. doi: 10.1155/2013/609581. Epub 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1155/2013/609581](#)

**AUTORES / AUTHORS:** - Tang YQ; Jaganath I; Manikam R; Sekaran SD

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Microbiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

**RESUMEN / SUMMARY:** - Phyllanthus is a traditional medicinal plant that has been found to have antihepatitis, antibacterial, and anticancer properties. The present studies were to investigate the in vitro molecular mechanisms of anticancer effects of Phyllanthus (*P. amarus*, *P. niruri*, *P. urinaria*, and *P. watsonii*) plant extracts in human prostate adenocarcinoma. The cancer ten-pathway reporter array was performed and revealed that the expression of six pathway reporters were significantly decreased (Wnt, NFkappaB, Myc/Max, hypoxia, MAPK/ERK, and MAPK/JNK) in PC-3 cells after treatment with Phyllanthus extracts. Western blot was conducted and identified several signalling molecules that were affected in the signalling pathways including pan-Ras, c-Raf, RSK, Elk1, c-Jun, JNK1/2, p38 MAPK, c-myc, DSH, beta-catenin, Akt, HIF-1alpha, GSK3beta, NFkappaB p50 and p52, Bcl-2, Bax, and VEGF, in treated PC-3 cells. A proteomics-based approach, 2D gel electrophoresis, was performed, and mass spectrometry (MS/MS) results revealed that there were 72 differentially expressed proteins identified in treated PC-3 cells and were involved in tumour cell adhesion, apoptosis, glycogenesis and glycolysis, metastasis, angiogenesis, and protein synthesis and energy metabolism. Overall, these findings suggest that Phyllanthus can interfere with multiple signalling cascades involved in tumorigenesis and be used as a potential therapeutic candidate for treatment of cancer.

[1174]

**TÍTULO / TITLE:** - -mannose-sensitive hemagglutinin inhibits proliferation and induces apoptosis in a caspase-dependent manner in human bladder cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Apr;5(4):1357-1362. Epub 2013 Feb 19.

●●Enlace al texto completo (gratis o de pago) [3892/ol.2013.1201](#)

**AUTORES / AUTHORS:** - Zhu YP; Bian XJ; Ye DW; Yao XD; Zhang SL; Dai B; Shen YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Fudan University Shanghai Cancer Center, Shanghai 200032, P.R. China ; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, P.R. China.

**RESUMEN / SUMMARY:** - The aim of the present study was to investigate the effects of *Pseudomonas aeruginosa*-mannose-sensitive hemagglutinin (PA-MSHA) on inhibiting the proliferation of bladder cancer cell lines and to further define its functional mechanisms. T24 and 5637 cells were treated with PA-MSHA at various concentrations and times. Cell proliferation was analyzed using Cell Counting Kit-8 (CCK-8) assays. The cell cycle distribution and apoptosis induced by PA-MSHA were measured by flow cytometry with propidium iodide (PI) and annexin V-fluorescein isothiocyanate (FITC) staining. Western blotting was used to evaluate the expression levels of the apoptosis-related molecules and PI3K-AKT-mTOR signaling pathway proteins. A time- and concentration-dependent cytotoxic effect of PA-MSHA was observed in the T24 and 5637 cells. Flow cytometry with PI and annexin V-FITC staining showed that the various concentrations of PA-MSHA were all able to induce the apoptosis and G0-G1 cell cycle arrest of the bladder cancer cells. Cleaved caspase-8 and -9 and Fas protein expression levels were markedly associated with an increase in the apoptosis of the bladder cancer cells. The cells stimulated with PA-MSHA also exhibited a downregulation of PI3K-AKT-mTOR signaling. PA-MSHA inhibits proliferation and induces apoptosis in the T24 and 5637 bladder cancer cell lines by modulating caspase family proteins and affecting the cell cycle regulation machinery. The PI3K-AKT-mTOR signaling pathway may be important in the direct anticancer cytotoxic effect of PA-MSHA.

[1175]

**TÍTULO / TITLE:** - Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Discov. 2013 Apr 25.

●●Enlace al texto completo (gratis o de pago) [1158/2159-8290.CD-13-0103](#)

**AUTORES / AUTHORS:** - Lui VW; Hedberg ML; Li H; Vangara BS; Pendleton K; Zeng Y; Lu Y; Zhang Q; Du Y; Gilbert B; Freilino M; Sauerwein S; Peyser N; Xiao D; Diergaarde B; Wang L; Chiosea S; Seethala RR; Johnson JT; Kim S; Duvvuri U; Ferris RL; Romkes M; Nukui T; Ng PK; Garraway LA; Hammerman P; Mills GB; Grandis JR

**INSTITUCIÓN / INSTITUTION:** - 1Otolaryngology, University of Pittsburgh.

**RESUMEN / SUMMARY:** - Genomic findings underscore the heterogeneity of head and neck squamous cell carcinoma (HNSCC)<sup>1,2</sup>. Identification of mutations that predict therapeutic response would be a major advance. We determined the mutationally altered, targetable mitogenic pathways in a large HNSCC cohort. Analysis of whole-exome sequencing data from 151 tumors revealed the PI3K pathway to be the most frequently mutated oncogenic pathway (30.5%). PI3K pathway-mutated HNSCC tumors harbored a significantly higher rate of mutations in known cancer genes. In a subset of HPV-positive tumors, PIK3CA or PIK3R1 was the only mutated cancer gene. Strikingly, all tumors with

concurrent mutation of multiple PI3K pathway genes were advanced (stage IV), implicating concerted PI3K pathway aberrations in HNSCC progression. Patient-derived tumorgrafts with canonical and non-canonical PIK3CA mutations were sensitive to an m-TOR/PI3K inhibitor (BEZ-235) in contrast to PIK3CA wildtype tumorgrafts. These results suggest that PI3K pathway mutations may serve as predictive biomarkers for treatment selection.

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[1176]

**TÍTULO / TITLE:** - Pomegranate Juice Metabolites, Ellagic Acid and Urolithin A, Synergistically Inhibit Androgen-Independent Prostate Cancer Cell Growth via Distinct Effects on Cell Cycle Control and Apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:247504. doi: 10.1155/2013/247504. Epub 2013 Apr 24.

●●Enlace al texto completo (gratis o de pago) [1155/2013/247504](#)

**AUTORES / AUTHORS:** - Vicinanza R; Zhang Y; Henning SM; Heber D

**INSTITUCIÓN / INSTITUTION:** - UCLA Center for Human Nutrition, David Geffen School of Medicine, University of California, Warren Hall, 900 Veteran Avenue 1-2-213, Los Angeles, CA 90095-1742, USA.

**RESUMEN / SUMMARY:** - Ellagitannins (ETs) from pomegranate juice (PJ) are bioactive polyphenols with chemopreventive potential against prostate cancer (PCa). ETs are not absorbed intact but are partially hydrolyzed in the gut to ellagic acid (EA). Colonic microflora can convert EA to urolithin A (UA), and EA and UA enter the circulation after PJ consumption. Here, we studied the effects of EA and UA on cell proliferation, cell cycle, and apoptosis in DU-145 and PC-3 androgen-independent PCa cells and whether combinations of EA and UA affected cell proliferation. EA demonstrated greater dose-dependent antiproliferative effects in both cell lines compared to UA. EA induced cell cycle arrest in S phase associated with decreased cyclin B1 and cyclin D1 levels. UA induced a G2/M arrest and increased cyclin B1 and cdc2 phosphorylation at tyrosine-15, suggesting inactivation of the cyclin B1/cdc2 kinase complex. EA induced apoptosis in both cell lines, while UA had a less pronounced proapoptotic effect only in DU-145. Cotreatment with low concentrations of EA and UA dramatically decreased cell proliferation, exhibiting synergism in PC-3 cells evaluated by isobolographic analysis and combination index. These data provide information on pomegranate metabolites for the prevention of PCa recurrence, supporting the role of gut flora-derived metabolites for cancer prevention.

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[1177]

**TÍTULO / TITLE:** - DNA methylation-based biomarkers in bladder cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nat Rev Urol. 2013 Apr 30. doi: 10.1038/nrurol.2013.89.

●●Enlace al texto completo (gratis o de pago) [1038/nrurol.2013.89](#)

**AUTORES / AUTHORS:** - Kandimalla R; van Tilborg AA; Zwarthoff EC

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Erasmus MC, P. O. Box 2040, 3000 CA Rotterdam, The Netherlands.

**RESUMEN / SUMMARY:** - Urinary bladder cancer is the fifth most common cancer in the Western world. Increasing evidence has shown that DNA methylation in bladder cancer is expansive and is implicated in pathogenesis. Furthermore, distinct methylation patterns have been identified between non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), as well as between FGFR3-mutant and wild-type tumours. Given these distinctions in expression, methylated genes have been proposed as diagnostic and prognostic biomarkers for patients with bladder cancer. Indeed, several studies have revealed that methylated genes-including CDH1, FHIT, LAMC2, RASSF1A, TIMP3, SFRP1, SOX9, PMF1 and RUNX3-are associated with poor survival in patients with MIBC. Further validation of these markers for prognostication as well as surveillance (of patients with NMIBC) is required. Validated markers for progression, diagnosis, survival and BCG response will contribute to clinical decision-making and individualized treatment.

[1178]

**TÍTULO / TITLE:** - Loss of runt-related transcription factor 3 induces gemcitabine resistance in pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Oncol. 2013 Apr 23. pii: S1574-7891(13)00065-3. doi: 10.1016/j.molonc.2013.04.004.

●●Enlace al texto completo (gratis o de pago)

[1016/j.molonc.2013.04.004](http://1016/j.molonc.2013.04.004)

**AUTORES / AUTHORS:** - Horiguchi S; Shiraha H; Nagahara T; Kataoka J; Iwamuro M; Matsubara M; Nishina S; Kato H; Takaki A; Nouse K; Tanaka T; Ichimura K; Yagi T; Yamamoto K

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND & AIM: Runt-related transcription factor 3 (RUNX3) is a tumor suppressor gene that is expressed in gastric and other cancers including pancreatic cancer. However, the precise function of RUNX3 in pancreatic cancer has not been fully elucidated. In this study, we aimed to determine the effect of decreased RUNX3 expression in pancreatic cancer. METHODS: This study included 36 patients with primary pancreatic cancer, who had undergone pancreaticoduodenectomy. All patients were treated with 1000 mg/m<sup>2</sup> gemcitabine after the surgery. The pancreatic cancer cell lines PANC-1, MIAPaCa-2, BxPC-3, SUIT-2, and KLM-1 were used for immunoblotting analysis of RUNX3 and multidrug resistance protein (MRP) expressions. Ectopic RUNX3 expression was achieved by cDNA transfection of

the cells, and small interfering RNA (siRNA) against RUNX3 was used to knock down endogenous RUNX3. Cell growth in the presence of gemcitabine was assessed using the MTT assay. RESULTS: Patients with RUNX3-positive and RUNX3-negative pancreatic cancer had a median survival of 1006 and 643 days, respectively. Exogenous RUNX3 expression reduced the expression of MRP1, MRP2, and MRP5 in endogenous RUNX3-negative cells, whereas RUNX3 siRNA increased the expressions of these genes in endogenous RUNX3-positive cells. Exogenous RUNX3 expression decreased gemcitabine IC50 in RUNX3-negative cells. CONCLUSION: Loss of RUNX3 expression contributes to gemcitabine resistance by inducing MRP expression, thereby resulting in poor patient survival.

[1179]

**TÍTULO / TITLE:** - Machine learning prediction of cancer cell sensitivity to drugs based on genomic and chemical properties.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 30;8(4):e61318. doi: 10.1371/journal.pone.0061318. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061318](https://doi.org/10.1371/journal.pone.0061318)

**AUTORES / AUTHORS:** - Menden MP; Iorio F; Garnett M; McDermott U; Benes CH; Ballester PJ; Saez-Rodriguez J

**INSTITUCIÓN / INSTITUTION:** - European Bioinformatics Institute, Wellcome Trust Genome Campus-Cambridge, Cambridge, United Kingdom.

**RESUMEN / SUMMARY:** - Predicting the response of a specific cancer to a therapy is a major goal in modern oncology that should ultimately lead to a personalised treatment. High-throughput screenings of potentially active compounds against a panel of genomically heterogeneous cancer cell lines have unveiled multiple relationships between genomic alterations and drug responses. Various computational approaches have been proposed to predict sensitivity based on genomic features, while others have used the chemical properties of the drugs to ascertain their effect. In an effort to integrate these complementary approaches, we developed machine learning models to predict the response of cancer cell lines to drug treatment, quantified through IC50 values, based on both the genomic features of the cell lines and the chemical properties of the considered drugs. Models predicted IC50 values in a 8-fold cross-validation and an independent blind test with coefficient of determination  $R^2$  of 0.72 and 0.64 respectively. Furthermore, models were able to predict with comparable accuracy ( $R^2$  of 0.61) IC50s of cell lines from a tissue not used in the training stage. Our in silico models can be used to optimise the experimental design of drug-cell screenings by estimating a large proportion of missing IC50 values rather than experimentally measuring them. The implications of our results go beyond virtual drug screening design: potentially thousands of drugs could be probed in silico to systematically test their potential

efficacy as anti-tumour agents based on their structure, thus providing a computational framework to identify new drug repositioning opportunities as well as ultimately be useful for personalized medicine by linking the genomic traits of patients to drug sensitivity.

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[1180]

**TÍTULO / TITLE:** - Oncomir miR-125b suppresses p14(ARF) to modulate p53-dependent and p53-independent apoptosis in prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 9;8(4):e61064. doi: 10.1371/journal.pone.0061064. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061064](#)

**AUTORES / AUTHORS:** - Amir S; Ma AH; Shi XB; Xue L; Kung HJ; Devere White RW

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, University of California Davis, Sacramento, California, United States of America.

**RESUMEN / SUMMARY:** - MicroRNAs are a class of naturally occurring small non-coding RNAs that target protein-coding mRNAs at the post-transcriptional level and regulate complex patterns of gene expression. Our previous studies demonstrated that in human prostate cancer the miRNA miR-125b is highly expressed, leading to a negative regulation of some tumor suppressor genes. In this study, we further extend our studies by showing that miR-125b represses the protein product of the ink4a/ARF locus, p14(ARF), in two prostate cancer cell lines, LNCaP (wild type-p53) and 22Rv1 (both wild type and mutant p53), as well as in the PC-346C prostate cancer xenograft model that lentivirally overexpressed miR-125b. Our results highlight that miR-125b modulates the p53 network by hindering the down-regulation of Mdm2, thereby affecting p53 and its target genes p21 and Puma to a degree sufficient to inhibit apoptosis. Conversely, treatment of prostate cancer cells with an inhibitor of miR-125b (anti-miR-125b) resulted in increased expression of p14(ARF), decreased level of Mdm2, and induction of apoptosis. In addition, overexpression of miR-125b in p53-deficient PC3 cells induced down-regulation of p14(ARF), which leads to increased cell proliferation through a p53-independent manner. Thus, we conclude that miR-125b acts as an oncogene which regulates p14(ARF)/Mdm2 signaling, stimulating proliferation of prostate cancer cells through a p53-dependent or p53-independent function. This reinforces our belief that miR-125b has potential as a therapeutic target for the management of patients with metastatic prostate cancer.

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[1181]

**TÍTULO / TITLE:** - Interplay between autophagy and apoptosis in pancreatic tumors in response to gemcitabine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Target Oncol. 2013 Apr 16.

●●Enlace al texto completo (gratis o de pago) [1007/s11523-013-0278-](http://1007/s11523-013-0278-5)

[5](#)

**AUTORES / AUTHORS:** - Papademetrio DL; Cavaliere V; Simunovich T; Costantino S; Campos MD; Lombardo T; Kaiser CM; Alvarez E

**INSTITUCIÓN / INSTITUTION:** - IDEHU-CONICET, Catedra de Inmunologia, Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Junin 956, 4 degrees piso, Ciudad Autonoma de Buenos Aires, Buenos Aires, Argentina, [dpapademetrio@ffyb.uba.ar](mailto:dpapademetrio@ffyb.uba.ar).

**RESUMEN / SUMMARY:** - Pancreatic cancer is an aggressive disease. Its incidence has increased over the last two decades. It is currently the fourth cause of death among cancers in the western world. Unfortunately, systemic chemotherapy still relies on just a few drugs which until now have produced unsatisfactory results. Gemcitabine (2'-2'-difluorodeoxycytidine) is currently the standard chemotherapy treatment at all stages of pancreatic adenocarcinoma. Survival benefit and clinical impact however remain moderate due to a high degree of intrinsic and acquired resistance. Autophagy plays an important role in cell death decision but can also protect cells from various apoptotic stimuli. We investigated the function of autophagy in pancreatic carcinoma cells, which are frequently insensitive to standard chemotherapeutic agents. Here, we demonstrate that autophagy is one of the mechanisms responsible for the refractory response of pancreatic tumors to gemcitabine. We present evidence in vitro and in vivo that proves autophagy plays a protective role in pancreatic ductal carcinoma cells, preventing them from entering the apoptotic pathway after stimulus with gemcitabine, thus contributing to treatment resistance. A better understanding of the role in the process may help in the discovery of new strategies to overcome tumor drug resistance in this aggressive disease.

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[1182]

**TÍTULO / TITLE:** - Prima-1 induces apoptosis in bladder cancer cell lines by activating p53.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clinics (Sao Paulo). 2013;68(3):297-303.

**AUTORES / AUTHORS:** - Piantino CB; Reis ST; Viana NI; Silva IA; Morais DR; Antunes AA; Dip N; Srougi M; Leite KR

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Medical Investigation, Urology Department - LIM55, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil.

**RESUMEN / SUMMARY:** - OBJECTIVES: Bladder cancer represents 3% of all carcinomas in the Brazilian population and ranks second in incidence among urological tumors, after prostate cancer. The loss of p53 function is the main genetic alteration related to the development of high-grade muscle-invasive disease. Prima-1 is a small molecule that restores tumor suppressor function to mutant p53 and induces cancer cell death in various cancer types. Our aim was

to investigate the ability of Prima-1 to induce apoptosis after DNA damage in bladder cancer cell lines. **METHOD:** The therapeutic effect of Prima-1 was studied in two bladder cancer cell lines: T24, which is characterized by a p53 mutation, and RT4, which is the wild-type for the p53 gene. Morphological features of apoptosis induced by p53, including mitochondrial membrane potential changes and the expression of thirteen genes involved in apoptosis, were assessed by microscopic observation and quantitative real-time PCR (qRT-PCR). **RESULTS:** Prima-1 was able to reactivate p53 function in the T24 (p53 mt) bladder cancer cell line and promote apoptosis via the induction of Bax and Puma expression, activation of the caspase cascade and disruption of the mitochondrial membrane in a BAK-independent manner. **CONCLUSION:** Prima-1 is able to restore the transcriptional activity of p53. Experimental studies in vivo may be conducted to test this molecule as a new therapeutic agent for urothelial carcinomas of the bladder, which characteristically harbor p53 mutations.

[1183]

**TÍTULO / TITLE:** - Apoptosis and other immune biomarkers predict influenza vaccine responsiveness.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Syst Biol. 2013 Apr 16;9:659. doi: 10.1038/msb.2013.15.

●●Enlace al texto completo (gratis o de pago) [1038/msb.2013.15](#)

**AUTORES / AUTHORS:** - Furman D; Jovic V; Kidd B; Shen-Orr S; Price J; Jarrell J; Tse T; Huang H; Lund P; Maecker HT; Utz PJ; Dekker CL; Koller D; Davis MM

**INSTITUCIÓN / INSTITUTION:** - Department of Microbiology and Immunology, School of Medicine, Stanford University, Palo Alto, CA 94305, USA.

**RESUMEN / SUMMARY:** - Despite the importance of the immune system in many diseases, there are currently no objective benchmarks of immunological health. In an effort to identifying such markers, we used influenza vaccination in 30 young (20-30 years) and 59 older subjects (60 to >89 years) as models for strong and weak immune responses, respectively, and assayed their serological responses to influenza strains as well as a wide variety of other parameters, including gene expression, antibodies to hemagglutinin peptides, serum cytokines, cell subset phenotypes and in vitro cytokine stimulation. Using machine learning, we identified nine variables that predict the antibody response with 84% accuracy. Two of these variables are involved in apoptosis, which positively associated with the response to vaccination and was confirmed to be a contributor to vaccine responsiveness in mice. The identification of these biomarkers provides new insights into what immune features may be most important for immune health.

[1184]

**TÍTULO / TITLE:** - A chemically sulfated polysaccharide from *Grifola frondosa* induces HepG2 cell apoptosis by notch1-NF-kappaB pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Carbohydr Polym. 2013 Jun 5;95(1):282-7. doi: 10.1016/j.carbpol.2013.02.057. Epub 2013 Mar 5.

●●Enlace al texto completo (gratis o de pago)

[1016/j.carbpol.2013.02.057](#)

**AUTORES / AUTHORS:** - Wang CL; Meng M; Liu SB; Wang LR; Hou LH; Cao XH

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Food Nutrition and Safety (Tianjin University of Science & Technology), Ministry of Education, Tianjin, China. Electronic address: [wangchunling@tust.edu.cn](mailto:wangchunling@tust.edu.cn).

**RESUMEN / SUMMARY:** - Sulfated polysaccharides have been known to inhibit proliferation in tumor cells. However, the molecular mechanisms involved in sulfated polysaccharides-induced apoptosis are still uncharacterized. In this study, the effect of a chemically sulfated polysaccharide obtained from *Grifola frondosa* (S-GFB) on HepG2 cell proliferation and apoptosis-related mechanism were investigated. It was found that S-GFB inhibited proliferation of HepG2 cells in a dose-dependent manner with IC50 at 48h of 61μgml(-1). The results of scanning electron micrographs indicated that S-GFB induced typical apoptotic morphological feature in HepG2 cells. Flow cytometric analysis demonstrated that S-GFB caused apoptosis of HepG2 cells through cells arrested at S phase. Western-blotting results showed that S-GFB inhibited notch1 expression, IκappaB-α degradation and NF-kappaB/p65 translocation from cytoplasm into nucleus. Simultaneously, the apoptotic mechanism of HepG2 cells induced by S-GFB was associated with down regulation of FLIP, and activation of caspase-3 and caspase-8. Taken together, these findings suggest that the S-GFB induces apoptosis through a notch1/NF-kappaB/p65-mediated caspase pathway.

[1185]

**TÍTULO / TITLE:** - Sh3glb1/Bif-1 and mitophagy: Acquisition of apoptosis resistance during Myc-driven lymphomagenesis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Autophagy. 2013 Apr 29;9(7).

**AUTORES / AUTHORS:** - Takahashi Y; Young MM; Serfass JM; Hori T; Wang HG

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology; Penn State Hershey Cancer Institute; Penn State College of Medicine; Hershey, PA USA.

**RESUMEN / SUMMARY:** - Evasion of apoptosis, which enables cells to survive and proliferate under metabolic stress, is one of the hallmarks of cancer. We have recently reported that SH3GLB1/Bif-1 functions as a haploinsufficient tumor suppressor to prevent the acquisition of apoptosis resistance and malignant transformation during Myc-driven lymphomagenesis. SH3GLB1 is a membrane curvature-inducing protein that interacts with BECN1 through UVRAG and regulates the post-Golgi trafficking of membrane-integrated

ATG9A for autophagy. At the premalignant stage, allelic loss of Sh3glb1 enhances Myc-induced chromosomal instability and results in the upregulation of anti-apoptotic proteins, including MCL1 and BCL2L1. Notably, we found that Sh3glb1 haploinsufficiency increases mitochondrial mass in overproliferated prelymphomatous Emu-Myc cells. Moreover, loss of Sh3glb1 suppresses autophagy-dependent mitochondrial clearance (mitophagy) in PARK2/Parkin-expressing mouse embryonic fibroblasts (MEFs) treated with the mitochondrial uncoupler CCCP. Interestingly, PARK2-expressing Sh3glb1-deficient cells accumulate ER-associated immature autophagosome-like structures after treatment with CCCP. Taken together, we propose a model of mitophagy in which SH3GLB1 together with the class III phosphatidylinositol 3-kinase complex II (PIK3C3CII) (PIK3R4-PIK3C3-BECN1-UVRAG) regulates the trafficking of ATG9A-containing Golgi-derived membranes (A9 (+) GDMs) to damaged mitochondria for autophagosome formation to counteract oncogene-driven tumorigenesis.

[1186]

**TÍTULO / TITLE:** - Hox-C9 activates the intrinsic pathway of apoptosis and is associated with spontaneous regression in neuroblastoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Apr 11;4:e586. doi: 10.1038/cddis.2013.84.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.84](#)

**AUTORES / AUTHORS:** - Kocak H; Ackermann S; Hero B; Kahlert Y; Oberthuer A; Juraeva D; Roels F; Theissen J; Westermann F; Deubzer H; Ehemann V; Brors B; Odenthal M; Berthold F; Fischer M

**INSTITUCIÓN / INSTITUTION:** - Children's Hospital, Department of Pediatric Oncology and Hematology and Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany.

**RESUMEN / SUMMARY:** - Neuroblastoma is an embryonal malignancy of the sympathetic nervous system. Spontaneous regression and differentiation of neuroblastoma is observed in a subset of patients, and has been suggested to represent delayed activation of physiologic molecular programs of fetal neuroblasts. Homeobox genes constitute an important family of transcription factors, which play a fundamental role in morphogenesis and cell differentiation during embryogenesis. In this study, we demonstrate that expression of the majority of the human HOX class I homeobox genes is significantly associated with clinical covariates in neuroblastoma using microarray expression data of 649 primary tumors. Moreover, a HOX gene expression-based classifier predicted neuroblastoma patient outcome independently of age, stage and MYCN amplification status. Among all HOX genes, HOXC9 expression was most prominently associated with favorable prognostic markers. Most notably, elevated HOXC9 expression was significantly associated with spontaneous regression in infant neuroblastoma. Re-expression of HOXC9 in three

neuroblastoma cell lines led to a significant reduction in cell viability, and abrogated tumor growth almost completely in neuroblastoma xenografts. Neuroblastoma growth arrest was related to the induction of programmed cell death, as indicated by an increase in the sub-G1 fraction and translocation of phosphatidylserine to the outer membrane. Programmed cell death was associated with the release of cytochrome c from the mitochondria into the cytosol and activation of the intrinsic cascade of caspases, indicating that HOXC9 re-expression triggers the intrinsic apoptotic pathway. Collectively, our results show a strong prognostic impact of HOX gene expression in neuroblastoma, and may point towards a role of Hox-C9 in neuroblastoma spontaneous regression.

[1187]

**TÍTULO / TITLE:** - Lovastatin induces apoptosis through the mitochondrial pathway in an undifferentiated SH-SY5Y neuroblastoma cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Apr 11;4:e585. doi: 10.1038/cddis.2013.112.

●●Enlace al texto completo (gratis o de pago) [1038/cddis.2013.112](http://1038/cddis.2013.112)

**AUTORES / AUTHORS:** - Marcuzzi A; Tricarico PM; Piscianz E; Kleiner G; Brumatti LV; Crovella S

[1188]

**TÍTULO / TITLE:** - Targeted Apoptotic Effects of Thymoquinone and Tamoxifen on XIAP Mediated Akt Regulation in Breast Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 17;8(4):e61342. doi: 10.1371/journal.pone.0061342. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061342](http://1371/journal.pone.0061342)

**AUTORES / AUTHORS:** - Rajput S; Kumar BN; Sarkar S; Das S; Azab B; Santhekadur PK; Das SK; Emdad L; Sarkar D; Fisher PB; Mandal M

**INSTITUCIÓN / INSTITUTION:** - School of Medical Science and Technology, Indian Institute of Technology Kharagpur, Kharagpur, West Bengal, India.

**RESUMEN / SUMMARY:** - X-linked inhibitor of apoptosis protein (XIAP) is constitutively expressed endogenous inhibitor of apoptosis, exhibit its antiapoptotic effect by inactivating key caspases such as caspase-3, caspase-7 and caspase-9 and also play pivotal role in rendering cancer chemoresistance. Our studies showed the coadministration of TQ and TAM resulting in a substantial increase in breast cancer cell apoptosis and marked inhibition of cell growth both in vitro and in vivo. Anti-angiogenic and anti-invasive potential of TQ and TAM was assessed through in vitro studies. This novel combinatorial regimen leads to regulation of multiple cell signaling targets including inactivation of Akt and XIAP degradation. At molecular level, TQ and TAM

synergistically lowers XIAP expression resulting in binding and activation of caspase-9 in apoptotic cascade, and interfere with cell survival through PI3-K/Akt pathway by inhibiting Akt phosphorylation. Cleaved caspase-9 further processes other intracellular death substrates such as PARP thereby shifting the balance from survival to apoptosis, indicated by rise in the sub-G1 cell population. This combination also downregulates the expression of Akt-regulated downstream effectors such as Bcl-xL, Bcl-2 and induce expression of Bax, AIF, cytochrome C and p-27. Consistent with these results, overexpression studies further confirmed the involvement of XIAP and its regulatory action on Akt phosphorylation along with procaspase-9 and PARP cleavage in TQ-TAM coadminstrated induced apoptosis. The ability of TQ and TAM in inhibiting XIAP was confirmed through siRNA-XIAP cotransfection studies. This novel modality may be a promising tool in breast cancer treatment.

[1189]

**TÍTULO / TITLE:** - Paclitaxel-induced apoptosis is BAK-dependent, but BAX and BIM-independent in breast tumor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013;8(4):e60685. doi: 10.1371/journal.pone.0060685. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060685](http://1371/journal.pone.0060685)

**AUTORES / AUTHORS:** - Miller AV; Hicks MA; Nakajima W; Richardson AC; Windle JJ; Harada H

**INSTITUCIÓN / INSTITUTION:** - Department of Oral and Craniofacial Molecular Biology, School of Dentistry, Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, USA.

**RESUMEN / SUMMARY:** - Paclitaxel (Taxol)-induced cell death requires the intrinsic cell death pathway, but the specific participants and the precise mechanisms are poorly understood. Previous studies indicate that a BH3-only protein BIM (BCL-2 Interacting Mediator of cell death) plays a role in paclitaxel-induced apoptosis. We show here that BIM is dispensable in apoptosis with paclitaxel treatment using bim(-/-) MEFs (mouse embryonic fibroblasts), the bim(-/-) mouse breast tumor model, and shRNA-mediated down-regulation of BIM in human breast cancer cells. In contrast, both bak (-/-) MEFs and human breast cancer cells in which BAK was down-regulated by shRNA were more resistant to paclitaxel. However, paclitaxel sensitivity was not affected in bax(-/-) MEFs or in human breast cancer cells in which BAX was down-regulated, suggesting that paclitaxel-induced apoptosis is BAK-dependent, but BAX-independent. In human breast cancer cells, paclitaxel treatment resulted in MCL-1 degradation which was prevented by a proteasome inhibitor, MG132. A Cdk inhibitor, roscovitine, blocked paclitaxel-induced MCL-1 degradation and apoptosis, suggesting that Cdk activation at mitotic arrest could induce subsequent MCL-1 degradation in a proteasome-dependent manner. BAK was

associated with MCL-1 in untreated cells and became activated in concert with loss of MCL-1 expression and its release from the complex. Our data suggest that BAK is the mediator of paclitaxel-induced apoptosis and could be an alternative target for overcoming paclitaxel resistance.

[1190]

**TÍTULO / TITLE:** - Novel Quinuclidinone Derivatives Induce Apoptosis in Lung Cancer via Sphingomyelinase Pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Drug Res (Stuttg). 2013 Apr 12.

●●Enlace al texto completo (gratis o de pago) [1055/s-0033-1341463](#)

**AUTORES / AUTHORS:** - Malki A; Fathy L; El Ashry ES

**INSTITUCIÓN / INSTITUTION:** - Biochemistry department, Faculty of Science, Alexandria University, Alexandria, Egypt.

**RESUMEN / SUMMARY:** - We previously reported novel quinuclidinone analogs which induced apoptosis in lung and breast cancer cells. In this study, we designed and synthesized novel quinuclidinone analogs that showed cytotoxicity in lung cancer cells. The effects of these analogs were studied in H1299 human large cell lung carcinoma cells that are null for p53 and normal lung epithelial cell lines (NL-20). The effects of the analogs were investigated by MTT assay, ELISA based apoptotic assay, TUNEL assay, sphingomyelinase activity, flow cytometry and western blot analysis. Our data indicated that derivatives 4 and 6 decreased cell proliferation and induced apoptosis in H1299 cells more than NL-20 cells. Derivatives 4 and 6 reduced percent of cells in G2/M phase in H1299 cells more than NL-20 cells and these results were confirmed by increased expression levels of cyclin E. Furthermore, derivatives 4 and 6 increased sphingomyelinase activity, caspase-8, and caspase-9 and JNK-1 expression level in H1299. Additionally, derivatives 4 and 6 induced Procaspase-3, PARP-1 cleavage, and increased caspase-3 activity. All these results confirm that our quinuclidinone derivatives provoke cytotoxicity in lung cancer cells through the interplay of key apoptosis molecules in different compartments of the cell beginning with an increase in sphingomyelinase activity.

[1191]

**TÍTULO / TITLE:** - MicroRNA-143 inhibits tumor growth and angiogenesis and sensitizes chemosensitivity to oxaliplatin in colorectal cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Cycle. 2013 May 1;12(9):1385-94. doi: 10.4161/cc.24477. Epub 2013 Apr 8.

●●Enlace al texto completo (gratis o de pago) [4161/cc.24477](#)

**AUTORES / AUTHORS:** - Qian X; Yu J; Yin Y; He J; Wang L; Li Q; Zhang LQ; Li CY; Shi ZM; Xu Q; Li W; Lai LH; Liu LZ; Jiang BH

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology; State Key Lab of Reproductive Medicine and Cancer Center; Nanjing Medical University; Nanjing, China.

**RESUMEN / SUMMARY:** - Colorectal cancer (CRC) is one of the leading cancer-related causes of death in the world. Recently, downregulation of microRNA-143 (miR-143) has been observed in CRC tissues. Here in this study, we found that miR-143 expression was downregulated both in CRC patients' blood samples and tumor specimens. MiR-143 expression levels were strongly correlated with clinical stages and lymph node metastasis. Furthermore, insulin-like growth factor-I receptor (IGF-IR), a known oncogene, was a novel direct target of miR-143, whose expression levels were inversely correlated with miR-143 expression in human CRC specimens. Overexpression of miR-143 inhibited cell proliferation, migration, tumor growth and angiogenesis and increased chemosensitivity to oxaliplatin treatment in an IGF-IR-dependent manner. Taken together, these results revealed that miR-143 levels in human blood and tumor tissues are associated with CRC cancer occurrence, metastasis and drug resistance, and miR-143 levels may be used as a new diagnostic marker and therapeutic target for CRC in the future.

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[1192]

**TÍTULO / TITLE:** - S-adenosylmethionine, a methyl donor, up regulates tissue inhibitor of metalloproteinase-2 in colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Res. 2013 Apr 10;12(2):1106-18. doi: 10.4238/2013.April.10.6.

●●Enlace al texto completo (gratis o de pago) [4238/2013.April.10.6](#)

**AUTORES / AUTHORS:** - Hussain Z; Khan MI; Shahid M; Almajhdi FN

**INSTITUCIÓN / INSTITUTION:** - Center of Excellence in Biotechnology Research, King Saud University, Riyadh, Saudi Arabia. [hussainzahep@gmail.com](mailto:hussainzahep@gmail.com)

**RESUMEN / SUMMARY:** - DNA methylation is a fundamental epigenetic mechanism in regulating the expression of genes controlling crucial cell functions in cancer development. Gene silencing via CpG island methylation/demethylation in the promoter region is one of the mechanisms by which different genes are inactivated/activated in human cancers. Tissue inhibitor of metalloproteinase-2 (TIMP-2) is known to antagonize matrix metalloproteinase (MMP) activity and to suppress tumor growth, angiogenesis, invasion, and metastasis. TIMP-2 expression has been found to be both upregulated and downregulated in various cancers. The inconsistent TIMP-2 expression and unclear epigenetic regulation lead us to investigate its role in colorectal cancer in the presence of a methylating agent. Highly invasive human colorectal cells SW-620 were treated with the methyl donor S-adenosylmethionine (SAM) and its effect was evaluated by cell proliferation, cell cycle, invasion and migration assay. The ability of SAM to down regulate a panel of activated prometastatic, angiogenesis and growth- and cell cycle-

regulatory genes was evaluated using end-point and real-time PCR. Treatment of SW-620 with SAM diminished cell proliferation and altered cell cycle kinetic G2/M phase cell cycle arrest. An in vitro matrigel invasion assay of SAM-treated cells showed a significant reduction in the invasive potential compared to untreated SW-620 cells. Treatment of SW-620 cells with SAM resulted in activation of TIMP-2 and inhibition of the expression of genes such as MMP (MMP-2, MT1-MMP), urokinase plasminogen activator, and vascular endothelial growth factors. The level of expression of tumor suppressor and apoptotic genes was not significantly higher compared to the untreated control. No changes in the levels of expression of genes (growth and cell cycle regulator), such as TGF-beta, Smad2, Smad4, and p21 were observed. Our data support the hypothesis that TIMP-2, along with other prometastatic genes, is hypomethylated and expressed differently in colorectal cancer. Further in-depth analysis is warranted to confirm the promoter region CpG methylation pattern of the TIMP-2 gene.

[1193]

**TÍTULO / TITLE:** - Cancer pain.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Opin Support Palliat Care. 2013 Jun;7(2):139-43. doi: 10.1097/SPC.0b013e3283610433.

●●Enlace al texto completo (gratis o de pago)

[1097/SPC.0b013e3283610433](#)

**AUTORES / AUTHORS:** - Mercadante S

**INSTITUCIÓN / INSTITUTION:** - aAnesthesia and Intensive Care Unit and Pain Relief and Palliative Care Unit, La Maddalena Cancer Center bDepartment of Palliative Medicine, University of Palermo, Palermo, Italy.

**RESUMEN / SUMMARY:** - PURPOSE OF REVIEW: Cancer pain management is in continuous innovation and new data are available that could change the therapeutic approach and guidelines. RECENT FINDINGS: There are different fields of research that produce new data and interesting findings. The principal data regard the factors influencing the analgesic response, breakthrough cancer pain management, opioid switching, and pharmacogenetics. SUMMARY: The findings reported in this review provide new ideas to be developed in further studies to confirm or not confirm some suggestive data.

[1194]

**TÍTULO / TITLE:** - Honokiol inhibits non-small cell lung cancer cell migration by targeting PGE(2)-mediated activation of beta-catenin signaling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 8;8(4):e60749. doi: 10.1371/journal.pone.0060749. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0060749](#)

**AUTORES / AUTHORS:** - Singh T; Katiyar SK

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, University of Alabama at Birmingham, Birmingham, Alabama, United States of America.

**RESUMEN / SUMMARY:** - Lung cancer remains a leading cause of death due to its metastasis to distant organs. We have examined the effect of honokiol, a bioactive constituent from the Magnolia plant, on human non-small cell lung cancer (NSCLC) cell migration and the molecular mechanisms underlying this effect. Using an in vitro cell migration assay, we found that treatment of A549, H1299, H460 and H226 NSCLC cells with honokiol resulted in inhibition of migration of these cells in a dose-dependent manner, which was associated with a reduction in the levels of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2). Celecoxib, a COX-2 inhibitor, also inhibited cell migration. Honokiol inhibited PGE2-enhanced migration of NSCLC cells, inhibited the activation of NF-kappaB/p65, an upstream regulator of COX-2, in A549 and H1299 cells, and treatment of cells with caffeic acid phenethyl ester, an inhibitor of NF-kappaB, also inhibited migration of NSCLC cells. PGE2 has been shown to activate beta-catenin signaling, which contributes to cancer cell migration. Therefore, we checked the effect of honokiol on beta-catenin signaling. It was observed that treatment of NSCLC cells with honokiol degraded cytosolic beta-catenin, reduced nuclear accumulation of beta-catenin and down-regulated matrix metalloproteinase (MMP)-2 and MMP-9, which are the down-stream targets of beta-catenin and play a crucial role in cancer cell metastasis. Honokiol enhanced: (i) the levels of casein kinase-1alpha, glycogen synthase kinase-3beta, and (ii) phosphorylation of beta-catenin on critical residues Ser(45), Ser(33/37) and Thr(41). These events play important roles in degradation or inactivation of beta-catenin. Treatment of celecoxib also reduced nuclear accumulation of beta-catenin in NSCLC cells. FH535, an inhibitor of Wnt/beta-catenin pathway, inhibited PGE2-enhanced cell migration of A549 and H1299 cells. These results indicate that honokiol inhibits non-small cell lung cancer cells migration by targeting PGE2-mediated activation of beta-catenin signaling.

[1195]

**TÍTULO / TITLE:** - NMR Metabolomics Analysis of the Effects of 5-Lipoxygenase Inhibitors on Metabolism in Glioblastomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Proteome Res. 2013 May 3;12(5):2165-2176. Epub 2013 Apr 22.

●●Enlace al texto completo (gratis o de pago) [1021/pr400026q](#)

**AUTORES / AUTHORS:** - Morin PJ; Ferguson D; Leblanc LM; Hebert MJ; Pare AF; Jean-Francois J; Surette ME; Touaibia M; Cuperlovic-Culf M

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry and Biochemistry, Universite de Moncton , Moncton, Canada.

**RESUMEN / SUMMARY:** - Changes across metabolic networks are emerging as an integral part of cancer development and progression. Increasing

comprehension of the importance of metabolic processes as well as metabolites in cancer is stimulating exploration of novel, targeted treatment options. Arachidonic acid (AA) is a major component of phospholipids. Through the cascade catalyzed by cyclooxygenases and lipoxygenases, AA is also a precursor to cellular signaling molecules as well as molecules associated with a variety of diseases including cancer. 5-Lipoxygenase catalyzes the transformation of AA into leukotrienes (LT), important mediators of inflammation. High-throughput analysis of metabolic profiles was used to investigate the response of glioblastoma cell lines to treatment with 5-lipoxygenase inhibitors. Metabolic profiling of cells following drug treatment provides valuable information about the response and metabolic alterations induced by the drug action and give an indication of both on-target and off-target effects of drugs. Four different 5-lipoxygenase inhibitors and antioxidants were tested including zileuton, caffeic acid, and its analogues caffeic acid phenethyl ester and caffeic acid cyclohexethyl ester. A NMR approach identified metabolic signatures resulting from application of these compounds to glioblastoma cell lines, and metabolic data were used to develop a better understanding of the mode of action of these inhibitors.

[1196]

**TÍTULO / TITLE:** - A combined 3D-QSAR and docking studies for the In-silico prediction of HIV-protease inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chem Cent J. 2013 May 17;7(1):88. doi: 10.1186/1752-153X-7-88.

●●Enlace al texto completo (gratis o de pago) [1186/1752-153X-7-88](#)

**AUTORES / AUTHORS:** - Ul-Haq Z; Usmani S; Shamshad H; Mahmood U; Halim SA

**INSTITUCIÓN / INSTITUTION:** - Dr, Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan. [zaheer.gasmi@iccs.edu](mailto:zaheer.gasmi@iccs.edu).

**RESUMEN / SUMMARY:** - BACKGROUND: Tremendous research from last twenty years has been pursued to cure human life against HIV virus. A large number of HIV protease inhibitors are in clinical trials but still it is an interesting target for researchers due to the viral ability to get mutated. Mutated viral strains led the drug ineffective but still used to increase the life span of HIV patients.

RESULTS: In the present work, 3D-QSAR and docking studies were performed on a series of Danuravir derivatives, the most potent HIV- protease inhibitor known so far. Combined study of 3D-QSAR was applied for Danuravir derivatives using ligand-based and receptor-based protocols and generated models were compared. The results were in good agreement with the experimental results. Additionally, docking analysis of most active 32 and least active 46 compounds into wild type and mutated protein structures further verified our results. The 3D-QSAR and docking results revealed that compound

32 bind efficiently to the wild and mutated protein whereas, sufficient interactions were lost in compound 46. CONCLUSION: The combination of two computational techniques would help to make a clear decision that compound 32 with well inhibitory activity binds more efficiently within the binding pocket even in case of mutant virus whereas compound 46 lost its interactions on mutation and marked as least active compound of the series. This is all due to the presence or absence of substituents on core structure, evaluated by 3D-QSAR studies. This set of information could be used to design highly potent drug candidates for both wild and mutated form of viruses.

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[1197]

**TÍTULO / TITLE:** - Mutant p53 Attenuates the Anti-Tumorigenic Activity of Fibroblasts-Secreted Interferon Beta.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 22;8(4):e61353. doi: 10.1371/journal.pone.0061353. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061353](http://1371/journal.pone.0061353)

**AUTORES / AUTHORS:** - Madar S; Harel E; Goldstein I; Stein Y; Kogan-Sakin I; Kamer I; Solomon H; Dekel E; Tal P; Goldfinger N; Friedlander G; Rotter V

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel.

**RESUMEN / SUMMARY:** - Mutations in the p53 tumor suppressor protein are highly frequent in tumors and often endow cells with tumorigenic capacities. We sought to examine a possible role for mutant p53 in the cross-talk between cancer cells and their surrounding stroma, which is a crucial factor affecting tumor outcome. Here we present a novel model which enables individual monitoring of the response of cancer cells and stromal cells (fibroblasts) to co-culturing. We found that fibroblasts elicit the interferon beta (IFNbeta) pathway when in contact with cancer cells, thereby inhibiting their migration. Mutant p53 in the tumor was able to alleviate this response via SOCS1 mediated inhibition of STAT1 phosphorylation. IFNbeta on the other hand, reduced mutant p53 RNA levels by restricting its RNA stabilizer, WIG1. These data underscore mutant p53 oncogenic properties in the context of the tumor microenvironment and suggest that mutant p53 positive cancer patients might benefit from IFNbeta treatment.

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[1198]

**TÍTULO / TITLE:** - mTOR Inhibitors Control the Growth of EGFR Mutant Lung Cancer Even after Acquiring Resistance by HGF.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 May 14;8(5):e62104. doi: 10.1371/journal.pone.0062104. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062104](https://doi.org/10.1371/journal.pone.0062104)

**AUTORES / AUTHORS:** - Ishikawa D; Takeuchi S; Nakagawa T; Sano T; Nakade J; Nanjo S; Yamada T; Ebi H; Zhao L; Yasumoto K; Nakamura T; Matsumoto K; Kagamu H; Yoshizawa H; Yano S

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Kanazawa, Japan ; Department of Medicine (II), Niigata University Medical and Dental Hospital, Niigata City, Japan.

**RESUMEN / SUMMARY:** - Resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), gefitinib and erlotinib, is a critical problem in the treatment of EGFR mutant lung cancer. Several mechanisms, including bypass signaling by hepatocyte growth factor (HGF)-triggered Met activation, are implicated as mediators of resistance. The mammalian target of rapamycin (mTOR), is a downstream conduit of EGFR and MET signaling, and is thus considered a therapeutically attractive target in the treatment of various types of cancers. The purpose of this study was to examine whether 2 clinically approved mTOR inhibitors, temsirolimus and everolimus, overcome HGF-dependent resistance to EGFR-TKIs in EGFR mutant lung cancer cells. Both temsirolimus and everolimus inhibited the phosphorylation of p70S6K and 4E-BP1, which are downstream targets of the mTOR pathway, and reduced the viability of EGFR mutant lung cancer cells, PC-9, and HCC827, even in the presence of HGF in vitro. In a xenograft model, temsirolimus suppressed the growth of PC-9 cells overexpressing the HGF-gene; this was associated with suppression of the mTOR signaling pathway and tumor angiogenesis. In contrast, erlotinib did not suppress this signaling pathway or tumor growth. Multiple mechanisms, including the inhibition of vascular endothelial growth factor production by tumor cells and suppression of endothelial cell viability, contribute to the anti-angiogenic effect of temsirolimus. These findings indicate that mTOR inhibitors may be useful for controlling HGF-triggered EGFR-TKI resistance in EGFR mutant lung cancer, and they provide the rationale for clinical trials of mTOR inhibitors in patients stratified by EGFR mutation and HGF expression status.

[1199]

**TÍTULO / TITLE:** - Intra-lesional interferon injection for recurrent conjunctival MALT lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eye (Lond). 2013 May;27(5):680-2. doi: 10.1038/eye.2013.46. Epub 2013 Apr 5.

●●Enlace al texto completo (gratis o de pago) [1038/eye.2013.46](https://doi.org/10.1038/eye.2013.46)

**AUTORES / AUTHORS:** - Zayed M; Sears K; Salvi SM; Rundle PA; Rennie IG; Mudhar HS

**INSTITUCIÓN / INSTITUTION:** - Ophthalmology Department, Royal Hallamshire Hospital, Sheffield, UK.

[1200]

**TÍTULO / TITLE:** - Inhibition of endotrophin, a cleavage product of collagen VI, confers cisplatin sensitivity to tumours.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - EMBO Mol Med. 2013 Jun;5(6):935-48. doi: 10.1002/emmm.201202006. Epub 2013 Apr 30.

●●Enlace al texto completo (gratis o de pago) [1002/emmm.201202006](#)

**AUTORES / AUTHORS:** - Park J; Morley TS; Scherer PE

**INSTITUCIÓN / INSTITUTION:** - Departments of Internal Medicine, Touchstone Diabetes Center, The University of Texas Southwestern Medical Center, Dallas, TX, USA.

**RESUMEN / SUMMARY:** - Endotrophin is a cleavage product of collagenVIalpha3 (COL6A3). Here, we explore the relationship between thiazolidinediones (TZDs), endotrophin and cisplatin resistance in the context of a mammary tumour model. COL6A3 levels are increased in response to cisplatin exposure in tumours. Endotrophin, in turn, causes cisplatin resistance. The effects of endotrophin can be bypassed, either through use of COL6 null (COL6(-/-) ) mice or by administering TZDs in wild-type mice (leading to a downregulation of endotrophin). Both approaches sensitize tumours to cisplatin through the suppression of endotrophin-induced epithelial-mesenchymal transition. The beneficial effects of TZDs on cisplatin sensitivity are diminished in COL6(-/-) mice, whereas endotrophin(+) tumours are sensitive to the TZD/cisplatin combination. Therefore, the chemosensitization obtained with TZDs is achieved through a downregulation of endotrophin. Treatment with an endotrophin neutralizing antibody in combination with cisplatin completely inhibits tumour growth of tumour allografts. Combined, our data suggest that endotrophin levels are a strong prognostic marker for the effectiveness of the combination therapy of TZDs with cisplatin, and neutralization of endotrophin activity dramatically improves the therapeutic response to combination therapy.

[1201]

**TÍTULO / TITLE:** - Role of beta4 integrin in HER-3-negative, K-RAS wild-type metastatic colorectal tumors receiving cetuximab.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 Apr 26.

●●Enlace al texto completo (gratis o de pago) [2217/fon.13.72](#)

**AUTORES / AUTHORS:** - Scartozzi M; Giampieri R; Loretelli C; Mandolesi A; Del Prete M; Biagetti S; Alfonsi S; Faloppi L; Bianconi M; Bittoni A; Bearzi I; Cascinu S

**INSTITUCIÓN / INSTITUTION:** - Clinica di Oncologia Medica, AO Ospedali Riuniti-Universita Politecnica delle Marche, Ancona, Italy.

**RESUMEN / SUMMARY:** - Aims: Altered alpha6beta4 integrin expression has been demonstrated in HER-3-negative tumors and may be responsible for anti-HER

treatment resistance. The current study aimed to evaluate the interaction between polymorphisms of alpha6 and beta4 integrins and clinical outcome in HER-3-negative, K-RAS wild-type colorectal cancer patients receiving cetuximab. Patients & methods:K-RAS analysis was performed via direct sequencing, HER-3 was evaluated by immunohistochemistry and genotyping of alpha6 and beta4 integrins was performed by real-time PCR. Results: An univariate analysis, the beta4 rs8669, rs871443 and rs9367 polymorphisms correlated with progression-free and overall survival. On multivariate analysis, only the beta4 rs8669 maintained an independent role in influencing progression-free survival. Conclusion: We believe that beta4 rs8669 genotyping may help to identify a subgroup of HER-3-negative, K-RAS wild-type colorectal cancer patients who are more likely to benefit from anti-EGFR treatment. Our findings could also be relevant in planning future trials testing treatment strategies against the integrin-activated molecular pathways.

[1202]

**TÍTULO / TITLE:** - A Synthetic Podophyllotoxin Derivative Exerts Anti-Cancer Effects by Inducing Mitotic Arrest and Pro-Apoptotic ER Stress in Lung Cancer Preclinical Models.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 30;8(4):e62082. doi: 10.1371/journal.pone.0062082. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0062082](http://1371/journal.pone.0062082)

**AUTORES / AUTHORS:** - Chen JY; Tang YA; Li WS; Chiou YC; Shieh JM; Wang YC

**INSTITUCIÓN / INSTITUTION:** - Institute of Basic Medical Sciences, National Cheng Kung University, Tainan, Taiwan, R.O.C.

**RESUMEN / SUMMARY:** - Some potent chemotherapy drugs including tubulin-binding agents had been developed from nature plants, such as podophyllotoxin and paclitaxel. However, poor cytotoxic selectivity, serious side-effects, and limited effectiveness are still the major concerns in their therapeutic application. We developed a fully synthetic podophyllotoxin derivative named Ching001 and investigated its anti-tumor growth effects and mechanisms in lung cancer preclinical models. Ching001 showed a selective cytotoxicity to different lung cancer cell lines but not to normal lung cells. Ching001 inhibited the polymerization of microtubule resulting in mitotic arrest as evident by the accumulation of mitosis-related proteins, survivin and aurora B, thereby leading to DNA damage and apoptosis. Ching001 also activated pro-apoptotic ER stress signaling pathway. Intraperitoneal injection of 2 mg/kg Ching001 significantly inhibited the tumor growth of A549 xenograft, while injection of 0.2 mg/kg Ching001 decreased the lung colonization ability of A549 cells in experimental metastasis assay. These anti-tumor growth and lung colonization inhibition effects were stronger than those of paclitaxel treatment at the same

dosage. The xenograft tumor tissue stains further confirmed that Ching001 induced mitosis arrest and tumor apoptosis. In addition, the hematology and biochemistry tests of blood samples as well as tissue examinations indicated that Ching001 treatment did not show apparent organ toxicities in tested animals. We provided preclinical evidence that novel synthetic microtubule inhibitor Ching001, which can trigger DNA damage and apoptosis by inducing mitotic arrest and ER stress, is a potential anti-cancer compound for further drug development.

[1203]

**TÍTULO / TITLE:** - Folic acid conjugated guar gum nanoparticles for targeting methotrexate to colon cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Biomed Nanotechnol. 2013 Jan;9(1):96-106.

**AUTORES / AUTHORS:** - Sharma M; Malik R; Verma A; Dwivedi P; Banoth GS; Pandey N; Sarkar J; Mishra PR; Dwivedi AK

**INSTITUCIÓN / INSTITUTION:** - Pharmaceuticals Division, CSIR-Central Drug Research Institute, Chattar Manzil Palace, Lucknow 226001, India.

**RESUMEN / SUMMARY:** - It was envisaged to develop surface modified Guar Gum Nanoparticles (GGNP) with Folic acid (FA) charged with methotrexate (MTX) to target the colon specifically. The MTX loaded FA functionalized GGNP (MTX-FA-GGNP) have been prepared by emulsion crosslinking method. These surface modified nanoparticles were compared with unmodified MTX loaded GGNP (MTX-GGNP). The developed formulations were evaluated for size and size distribution, zeta potential, Differential Scanning Calorimetry (DSC), release profile and uptake studies. The nanoparticles have been found to have average size of 325 nm in diameter having polydispersity index (PDI) 0.177 indicating mono-disperse particles. The zeta potential of the particles was found to be -36.9 mV. The percent growth inhibition of Caco 2 cells with MTX-FA-GGNP was found to be better than MTX-GGNP indicating folate receptor mediated uptake. The MTX-GGNP protects the release of MTX in upper gastrointestinal tract while maximum release of MTX occurred in simulated colonic fluids of pH 6.8. The in vivo uptake studies revealed preferential uptake of nanoparticles formulation in the colon. These studies provide evidences that MTX-FA-GGNP holds promise to address colorectal cancer over-expressing folate receptors. This prototype formulation enjoys dual advantage of having propensity to release the drug in the colon and in the conditions of colorectal carcinoma; it could be better localized and targeted with improved therapy due to over-expression of folate receptors.

[1204]

**TÍTULO / TITLE:** - Novel acyclic nucleotide analogues GS-343074 and GS-424044 demonstrate antiproliferative and pro-apoptotic activity in canine neoplastic cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Vet Comp Oncol. 2013 May 15. doi: 10.1111/vco.12038.

●●Enlace al texto completo (gratis o de pago) [1111/vco.12038](#)

**AUTORES / AUTHORS:** - Lawrence JA; Huelsmeyer MK; Thamm DH; Tumas DB; Birkus G; Kurzman I; Vail DM

**INSTITUCIÓN / INSTITUTION:** - School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, USA.

**RESUMEN / SUMMARY:** - GS-9219, a novel prodrug of the nucleotide analogue 9-(2-phosphonylmethoxyethyl) guanine (PMEG) has significant activity as monotherapy in dogs with non-Hodgkin's lymphoma. Phase I trials have been initiated in humans based on the encouraging activity observed in canine lymphoma. Two new analogues of GS-9219 (GS-343074 and GS-424044) were recently produced for evaluation as potential novel antineoplastic agents against solid tumours. As a preclinical step, effect of GS-343074 and GS-424044 were evaluated against ten canine cancer cell lines for antiproliferative effect. Both analogues displayed antiproliferative activity against multiple canine cancer cell lines, although GS-343074 was more potent and of broader spectrum compared to GS-424044. Flow cytometric analysis of cells that experienced growth inhibition support apoptotic death as a mechanism of action for both analogues. On the basis of in vitro results described here, GS-343074 and GS-424044 show promise as novel anticancer agents in canine cancer.

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[1205]

**TÍTULO / TITLE:** - The histone deacetylase inhibitor valproic acid sensitizes diffuse large B-cell lymphoma cell lines to CHOP-induced cell death.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Transl Res. 2013;5(2):170-83. Epub 2013 Mar 28.

**AUTORES / AUTHORS:** - Ageberg M; Rydstrom K; Relander T; Drott K

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Transfusion Medicine, Lund University BMC B13, Klinikg. 26, S-22184 Lund, Sweden.

**RESUMEN / SUMMARY:** - Epigenetic code modifications by histone deacetylase inhibitors (HDACis) have recently been proposed as potential new therapies for hematological malignancies. Diffuse large B-cell lymphoma (DLBCL) is the most common form of aggressive lymphoma. At present, standard first line treatment for DLBCL patients is the anthracycline-based chemotherapy regimen CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) combined with the monoclonal anti-CD20 antibody rituximab (R-CHOP). Since only 50-60% of patients reach a long-time cure by this treatment, there is an urgent need for novel treatment strategies to increase the response and long-term remission to initial R-CHOP therapy. In this study, we investigated the effect of the HDAC inhibitor valproic acid (VPA) on DLBCL cell lines. To elucidate the effects of VPA on chemo-sensitivity, we used a cell-line based model of CHOP-refractory DLBCL. All five DLBCL cell lines treated with VPA alone or in combination with CHOP showed decreased viability and proliferation. The VPA-induced

sensitization of DLBCL cells to cytotoxic treatment resulted in increased number of apoptotic cell as judged by annexin V-positivity and the presence of cleaved caspase-3. In addition, pretreatment with VPA resulted in a significantly increased DNA-damage as compared to CHOP alone. In summary, HDAC inhibitors such as VPA, are promising therapeutic agents in combination with R-CHOP for patients with DLBCL.

[1206]

**TÍTULO / TITLE:** - Cytotoxic effects of palladium (II) and platinum (II) complexes with O,O'-dialkyl esters of (S,S)-ethylenediamine-N,N'-di-2-(4-methyl) pentanoic acid on human colon cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J BUON. 2013 Jan-Mar;18(1):131-7.

**AUTORES / AUTHORS:** - Volarevic V; Vujic JM; Milovanovic M; Kanjevac T; Volarevic A; Trifunovic SR; Arsenijevic N

**INSTITUCIÓN / INSTITUTION:** - Centre for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac;

**RESUMEN / SUMMARY:** - Summary Purpose: As novel therapeutic agents relevant to colon cancer therapy are explored continuously, we tested 4 R2edda-type ligand precursors O,O'-dialkyl esters of (S,S)-ethylenediamine-N,N'-di-2-(4-methyl)pentanoic acid (L1.2HCl-L4.2HCl) and corresponding palladium(II) and platinum(II) complexes against the human colon cancer cell lines CaCo-2, SW480 and HCT116. Methods: The effects of the tested compounds on cell viability were determined using MTT colorimetric technique. Results: Analysis of cancer cell viability showed that all tested ligand precursors, palladium(II) and platinum(II) complexes were cytotoxic on human colon cancer cells in dose-dependent manner. The cytotoxic activity of all palladium(II) and platinum(II) complexes toward selected cancer cells was significantly higher in comparison to cisplatin. Among the tested platinum(II) and palladium(II) complexes the lowest activity was observed for the compounds with the shortest ester chain and the highest activity was noted for palladium(II) complex No.2 with the n-Pr group in ester chain and for platinum(II) complex No.7 with the n-Bu group in ester chain. Conclusion: Palladium(II) complex No.2 and platinum(II) complex No.7 seem to be good candidates for future pharmacological evaluation in the field of colon cancer research and treatment.

[1207]

**TÍTULO / TITLE:** - Caveolin-1 is a negative regulator of tumor growth in glioblastoma and modulates chemosensitivity to temozolomide.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Cycle. 2013 May 15;12(10):1510-20. doi: 10.4161/cc.24497. Epub 2013 Apr 17.

●●Enlace al texto completo (gratis o de pago) [4161/cc.24497](https://doi.org/10.4161/cc.24497)

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**INSTITUCIÓN / INSTITUTION:** - Department of Stem Cell Biology & Regenerative Medicine; Kimmel Cancer Center; Thomas Jefferson University; Philadelphia, PA USA.

**RESUMEN / SUMMARY:** - Caveolin-1 (Cav-1) is a critical regulator of tumor progression in a variety of cancers where it has been shown to act as either a tumor suppressor or tumor promoter. In glioblastoma multiforme, it has been previously demonstrated to function as a putative tumor suppressor. Our studies here, using the human glioblastoma-derived cell line U-87MG, further support the role of Cav-1 as a negative regulator of tumor growth. Using a lentiviral transduction approach, we were able to stably overexpress Cav-1 in U-87MG cells. Gene expression microarray analyses demonstrated significant enrichment in gene signatures corresponding to downregulation of MAPK, PI3K/AKT and mTOR signaling, as well as activation of apoptotic pathways in Cav-1-overexpressing U-87MG cells. These same gene signatures were later confirmed at the protein level in vitro. To explore the ability of Cav-1 to regulate tumor growth in vivo, we further show that Cav-1-overexpressing U-87MG cells display reduced tumorigenicity in an ectopic xenograft mouse model, with marked hypoactivation of MAPK and PI3K/mTOR pathways. Finally, we demonstrate that Cav-1 overexpression confers sensitivity to the most commonly used chemotherapy for glioblastoma, temozolomide. In conclusion, Cav-1 negatively regulates key cell growth and survival pathways and may be an effective biomarker for predicting response to chemotherapy in glioblastoma.

[1208]

**TÍTULO / TITLE:** - Bladder cancer: Biomarker panel predicts recurrence after radical cystectomy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nat Rev Urol. 2013 Apr 23. doi: 10.1038/nrurol.2013.95.

●●Enlace al texto completo (gratis o de pago) [1038/nruol.2013.95](#)

**AUTORES / AUTHORS:** - Payton S

[1209]

**TÍTULO / TITLE:** - Anti-CD70 Immunocytokines for Exploitation of Interferon-gamma-Induced RIP1-Dependent Necrosis in Renal Cell Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Apr 17;8(4):e61446. doi: 10.1371/journal.pone.0061446. Print 2013.

●●Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0061446](#)

**AUTORES / AUTHORS:** - Chen P; Nogusa S; Thapa RJ; Shaller C; Simmons H; Peri S; Adams GP; Balachandran S

**INSTITUCIÓN / INSTITUTION:** - Immune Cell Development and Host Defense Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States of America.

**RESUMEN / SUMMARY:** - Metastatic renal cell carcinoma (RCC) is an incurable disease in clear need of new therapeutic interventions. In early-phase clinical trials, the cytokine IFN-gamma showed promise as a biotherapeutic for advanced RCC, but subsequent trials were less promising. These trials, however, focused on the indirect immunomodulatory properties of IFN-gamma, and its direct anti-tumor effects, including its ability to kill tumor cells, remains mostly unexploited. We have previously shown that IFN-gamma induces RIP1 kinase-dependent necrosis in cells lacking NF-kappaB survival signaling. RCC cells display basally-elevated NF-kappaB activity, and inhibiting NF-kappaB in these cells, for example by using the small-molecule proteasome blocker bortezomib, sensitizes them to RIP1-dependent necrotic death following exposure to IFN-gamma. While these observations suggest that IFN-gamma-mediated direct tumoricidal activity will have therapeutic benefit in RCC, they cannot be effectively exploited unless IFN-gamma is targeted to tumor cells in vivo. Here, we describe the generation and characterization of two novel 'immunocytokine' chimeric proteins, in which either human or murine IFN-gamma is fused to an antibody targeting the putative metastatic RCC biomarker CD70. These immunocytokines display high levels of species-specific IFN-gamma activity and selective binding to CD70 on human RCC cells. Importantly, the IFN-gamma immunocytokines function as well as native IFN-gamma in inducing RIP1-dependent necrosis in RCC cells, when deployed in the presence of bortezomib. These results provide a foundation for the in vivo exploitation of IFN-gamma-driven tumoricidal activity in RCC.

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