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

Cancer Pharmacogenomics.

October / November 2013

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[1]

**TÍTULO / TITLE:** - A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias.

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

**REVISTA / JOURNAL:** - N Engl J Med. 2013 Nov 7;369(19):1783-96. doi: 10.1056/NEJMoa1306494. Epub 2013 Nov 1.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMoa1306494](#)

**AUTORES / AUTHORS:** - Cortes JE; Kim DW; Pinilla-Ibarz J; le Coutre P; Paquette R; Chuah C; Nicolini FE; Apperley JF; Khoury HJ; Talpaz M; DiPersio J; DeAngelo DJ; Abruzzese E; Rea D; Baccarani M; Muller MC; Gambacorti-Passerini C; Wong S; Lustgarten S; Rivera VM; Clackson T; Turner CD; Haluska FG; Guilhot F; Deininger MW; Hochhaus A; Hughes T; Goldman JM; Shah NP; Kantarjian H

**INSTITUCIÓN / INSTITUTION:** - The authors' full names, degrees, and affiliations are listed in the Appendix.

**RESUMEN / SUMMARY:** - BACKGROUND: Ponatinib is a potent oral tyrosine kinase inhibitor of unmutated and mutated BCR-ABL, including BCR-ABL with the tyrosine kinase inhibitor-refractory threonine-to-isoleucine mutation at position 315 (T315I). We conducted a phase 2 trial of ponatinib in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL). METHODS: We enrolled 449 heavily pretreated patients who had CML or Ph-positive ALL with resistance to or unacceptable side effects from dasatinib or nilotinib or who had the BCR-ABL T315I mutation. Ponatinib was administered at an initial dose of 45 mg once daily. The median follow-up was 15 months. RESULTS: Among 267 patients with chronic-phase CML, 56% had a major cytogenetic response (51% of patients with resistance to or unacceptable side effects from dasatinib or nilotinib and 70% of

patients with the T315I mutation), 46% had a complete cytogenetic response (40% and 66% in the two subgroups, respectively), and 34% had a major molecular response (27% and 56% in the two subgroups, respectively). Responses were observed regardless of the baseline BCR-ABL kinase domain mutation status and were durable; the estimated rate of a sustained major cytogenetic response of at least 12 months was 91%. No single BCR-ABL mutation conferring resistance to ponatinib was detected. Among 83 patients with accelerated-phase CML, 55% had a major hematologic response and 39% had a major cytogenetic response. Among 62 patients with blast-phase CML, 31% had a major hematologic response and 23% had a major cytogenetic response. Among 32 patients with Ph-positive ALL, 41% had a major hematologic response and 47% had a major cytogenetic response. Common adverse events were thrombocytopenia (in 37% of patients), rash (in 34%), dry skin (in 32%), and abdominal pain (in 22%). Serious arterial thrombotic events were observed in 9% of patients; these events were considered to be treatment-related in 3%. A total of 12% of patients discontinued treatment because of an adverse event. CONCLUSIONS: Ponatinib had significant antileukemic activity across categories of disease stage and mutation status. (Funded by Ariad Pharmaceuticals and others; PACE ClinicalTrials.gov number, NCT01207440 .).

[2]

**TÍTULO / TITLE:** - Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.

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

**REVISTA / JOURNAL:** - N Engl J Med. 2013 Oct 31;369(18):1691-703. doi: 10.1056/NEJMoa1304369. Epub 2013 Oct 16.

●● [Enlace al texto completo \(gratis o de pago\) 1056/NEJMoa1304369](#)

**AUTORES / AUTHORS:** - Von Hoff DD; Ervin T; Arena FP; Chiorean EG; Infante J; Moore M; Seay T; Tjulandin SA; Ma WW; Saleh MN; Harris M; Reni M; Dowden S; Laheru D; Bahary N; Ramanathan RK; Tabernero J; Hidalgo M; Goldstein D; Van Cutsem E; Wei X; Iglesias J; Renschler MF

**INSTITUCIÓN / INSTITUTION:** - From the Translational Genomics Research Institute, Phoenix, and Virginia G. Piper Cancer Center, Scottsdale - both in Arizona (D.D.V.H., R.K.R.); Cancer Specialists, Fort Myers, FL (T.E.); Arena Oncology Associates, Lake Success (F.P.A.), and Roswell Park Cancer Institute, Buffalo (W.W.M.) - both in New York; University of Washington, Seattle (E.G.C.); Sarah Cannon Research Institute-Tennessee Oncology, Nashville (J. Infante); Princess Margaret Hospital, Toronto (M.M.); Atlanta Cancer Care (T.S.) and Georgia Cancer Specialists (M.N.S.) - both in Atlanta; Blokhin Cancer Research Center, Moscow (S.A.T.); Southern Health, East Bentleigh, VIC (M.H.), Prince of Wales Hospital, Sydney (D.G.), and Bionomics, Thebarton, SA (J. Iglesias) - all in Australia; San Raffaele Scientific Institute, Milan (M.R.); Tom Baker Cancer Centre, Calgary, AB, Canada (S.D.); Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore (D.L.); University of Pittsburgh Medical Center, Pittsburgh (N.B.); Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona (J.T.); Centro Integral Oncológico Clara Campal, Madrid (M.H.); University Hospitals Leuven and Katholieke Universiteit Leuven, Leuven, Belgium (E.V.C.); and Celgene, Summit, NJ (X.W., M.F.R.).

**RESUMEN / SUMMARY:** - BACKGROUND: In a phase 1-2 trial of albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine, substantial clinical activity was noted in patients with advanced pancreatic cancer. We conducted a phase 3 study of the efficacy and safety of the combination versus gemcitabine monotherapy in patients with metastatic pancreatic cancer. METHODS: We randomly assigned patients with a Karnofsky performance-status score of 70 or more (on a scale from 0 to 100, with higher scores indicating better performance status) to nab-paclitaxel (125 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter) on days 1, 8, and 15 every 4 weeks or gemcitabine monotherapy (1000 mg per square meter) weekly for 7 of 8 weeks (cycle 1) and then on days 1, 8, and 15 every 4 weeks (cycle 2 and subsequent cycles). Patients received the study treatment until disease progression. The primary end point was overall survival; secondary end points were progression-free survival and overall response rate. RESULTS: A total of 861 patients were randomly assigned to nab-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median overall survival was 8.5 months in the nab-paclitaxel-gemcitabine group as compared with 6.7 months in the gemcitabine group (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 35% in the nab-paclitaxel-gemcitabine group versus 22% in the gemcitabine group at 1 year, and 9% versus 4% at 2 years. The median progression-free survival was 5.5 months in the nab-paclitaxel-gemcitabine group, as compared with 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were neutropenia (38% in the nab-paclitaxel-gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). Febrile neutropenia occurred in 3% versus 1% of the patients in the two groups. In the nab-paclitaxel-gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days. CONCLUSIONS: In patients with metastatic pancreatic adenocarcinoma, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased. (Funded by Celgene; ClinicalTrials.gov number, NCT00844649.).

[3]

**TÍTULO / TITLE:** - A phase 2 trial of azacitidine and gemtuzumab ozogamicin therapy in older patients with acute myeloid leukemia.

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

**REVISTA / JOURNAL:** - Blood. 2013 Nov 14;122(20):3432-9. doi: 10.1182/blood-2013-06-506592. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-06-506592](#)

**AUTORES / AUTHORS:** - Nand S; Othus M; Godwin JE; Willman CL; Norwood TH; Howard DS; Coutre SE; Erba HP; Appelbaum FR

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Loyola University Medical Center, Maywood, IL;

**RESUMEN / SUMMARY:** - This trial tested the safety and efficacy of a regimen consisting of hydroxyurea followed by azacitidine, 75 mg/m<sup>2</sup> for 7 days, and gemtuzumab ozogamicin, 3 mg/m<sup>2</sup> on day 8, in older patients with newly diagnosed

acute myeloid leukemia. Those achieving a complete remission received 1 consolidation treatment followed by 4 cycles of azacitidine. The patients were stratified into good-risk (age 60-69 years or performance status 0-1) and poor-risk (age  $\geq$ 70 years and performance status 2 or 3) groups. Specific efficacy and safety goals were defined as being supportive of further study of the regimen. Eighty-three patients were registered in the good-risk cohort and 59 in poor-risk cohort, with median age of 71 and 75 years, respectively. In the good-risk group, 35 patients (44%) achieved a complete remission. Median relapse-free and overall survivals were 8 and 11 months, respectively. Six patients (8%) died within 30 days of registration. In the poor-risk group, 19 (35%) achieved a complete remission. Median relapse-free and overall survivals were 7 and 11 months, respectively. Seven patients (14%) died early. The results of this trial met predefined goals for efficacy and safety for the poor-risk cohort but not the good-risk group. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as #NCT00658814.

[4]

**TÍTULO / TITLE:** - Adjuvant 5-fluorouracil, alpha-interferon and interleukin-2 versus observation in patients at high risk of recurrence after nephrectomy for renal cell carcinoma: Results of a Phase III randomised European Organisation for Research and Treatment of Cancer (Genito-Urinary Cancers Group)/National Cancer Research Institute trial.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Sep 25. pii: S0959-8049(13)00787-9. doi: 10.1016/j.ejca.2013.08.019.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ejca.2013.08.019](#)

**AUTORES / AUTHORS:** - Aitchison M; Bray CA; Van Poppel H; Sylvester R; Graham J; Innes C; McMahon L; Vasey PA

**INSTITUCIÓN / INSTITUTION:** - The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom. Electronic address: [michael.aitchison@nhs.net](mailto:michael.aitchison@nhs.net).

**RESUMEN / SUMMARY:** - BACKGROUND: The purpose of this trial was to compare adjuvant 5-fluorouracil, alpha-interferon and interleukin-2 to observation in patients at high risk of recurrence after nephrectomy for renal cell carcinoma (RCC) in terms of disease free survival, overall survival and quality of life (QoL). PATIENTS AND METHODS: Patients 8weeks post nephrectomy for RCC, without macroscopic residual disease, with stage T3b-c,T4 or any pT and pN1 or pN2 or positive microscopic margins or microscopic vascular invasion, and no metastases were randomised to receive adjuvant treatment or observation. QoL was assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-30 (QLQC-30). Treatment delivery and toxicity were monitored. The trial was designed to detect an increase in 3year disease free survival (DFS) from 50% on observation to 65% on treatment (hazard ratio (HR)=0.63) with 90% power and two-sided alpha=0.05. RESULTS: From 1998 to 2007, 309 patients were randomised (155 to observation; 154 to treatment). 35% did not complete the treatment, primarily due to toxicity (92% of patients experienced grade 2, 41% grade 3). Statistically significant differences between the arms in QoL parameters at 2months disappeared by 6months although there was suggestion of a persistent deficit in fatigue and physical function. Median follow-up was 7years (maximum 12.1years). 182 patients relapsed or died.

DFS at 3years was 50% with observation and 61% with treatment (HR 0.84, 95% confidence interval (CI) 0.63-1.12, p=0.233). 124 patients died. Overall survival (OS) at 5years was 63% with observation and 70% with treatment (HR 0.87, 95% CI 0.61-1.23, p=0.428). CONCLUSIONS: The treatment is associated with significant toxicity. There is no statistically significant benefit for the regimen in terms of disease free or overall survival.

[5]

**TÍTULO / TITLE:** - Clinical Characteristics and Long-Term Outcome of Young Hairy Cell Leukemia Patients Treated With Cladribine: A Single Institution Series.

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

**REVISTA / JOURNAL:** - Blood. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-06-508754](#)

**AUTORES / AUTHORS:** - Rosenberg JD; Burian C; Waalen J; Saven A

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology/Oncology, Scripps Clinic, La Jolla, CA, United States;

**RESUMEN / SUMMARY:** - Hairy cell leukemia (HCL) is a rare, indolent B-cell disorder in which single courses of cladribine induce high rates of complete responses. We report on 88 young HCL patients ( $\leq 40$  years at diagnosis) treated with cladribine from the Scripps Clinic HCL Database, of whom 83 were evaluable for response. 73 patients (88%) achieved an initial CR and 10 (12%) a PR, with a median response duration of 57 months. 48 patients (58%) relapsed, with a median time to first relapse for all responders of 54 months. 8 patients developed 11 second primary malignancies with an excess frequency of 1.60 (95% CI, 0.80 - 2.89). Thirteen (15%) patients died with a mortality ratio compared to age-matched normals of 1.85 (95% CI, 1.07 - 3.18). Median OS for all patients following the first cladribine course was 231 months, and 251 months from diagnosis. Single courses of cladribine induce high rates of complete and durable responses in the majority of young HCL patients, and is therefore recommended for HCL patients regardless of age.

[6]

**TÍTULO / TITLE:** - Longterm Effect of Delaying Combination Therapy with Tumor Necrosis Factor Inhibitor in Patients with Aggressive Early Rheumatoid Arthritis: 10-year Efficacy and Safety of Adalimumab from the Randomized Controlled PREMIER Trial with Open-label Extension.

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

**REVISTA / JOURNAL:** - J Rheumatol. 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [3899/jrheum.130543](#)

**AUTORES / AUTHORS:** - Keystone EC; Breedveld FC; van der Heijde D; Landewe R; Florentinus S; Arulmani U; Liu S; Kupper H; Kavanaugh A

**INSTITUCIÓN / INSTITUTION:** - From the University of Toronto, Toronto, Ontario, Canada; Leiden University Medical Center, Leiden, The Netherlands; Academic Medical Center, Amsterdam, The Netherlands; AbbVie, Rungis, France; AbbVie Inc., North Chicago, Illinois, USA; AbbVie Deutschland GmbH and Co KG, Ludwigshafen, Germany; University of California San Diego, La Jolla, California, USA.

**RESUMEN / SUMMARY:** - OBJECTIVE: To evaluate the longterm safety of adalimumab administered with or without methotrexate (MTX) and compare the efficacy of combination therapy initialization to adalimumab or MTX monotherapy initialization during the open-label extension (OLE) of the PREMIER trial (ClinicalTrials.gov Identifier:NCT00195663). METHODS: Patients with early rheumatoid arthritis (RA) were randomized to receive blinded adalimumab + MTX, adalimumab alone, or MTX alone for 2 years. Following the double-blinded period, patients enrolling in the OLE were given adalimumab for up to 8 additional years, beginning as monotherapy; investigators could add MTX at their discretion. Results for clinical, functional, and radiographic progression were collected for up to 10 years of treatment. RESULTS: During the PREMIER OLE, 250/497 patients (50.3%) completed the trial without new safety signals arising. Similar proportions of patients discontinued the trial early, although lack of efficacy was reported less often for patients initially randomized to the adalimumab + MTX arm (9.3%; 21.2%, and 23.7% for adalimumab and MTX monotherapies, respectively). Clinical and functional disease control was maintained throughout the trial. Patients initially randomized to adalimumab + MTX displayed better outcomes, particularly in prevention of radiographic progression (modified total Sharp score change = 4.0, 8.8, 11.0 at Year 10 for the initial adalimumab + MTX, adalimumab, and MTX arms, respectively). CONCLUSION: Intensive therapy with adalimumab + MTX combination in patients with early RA has longterm benefits compared to patients initiating with 2-year adalimumab or MTX monotherapy that persists up to 10 years following adalimumab OLE. No new safety findings were observed following longterm adalimumab treatment.

[7]

**TÍTULO / TITLE:** - Predictive and Prognostic Analysis of PIK3CA Mutation in Stage III Colon Cancer Intergroup Trial.

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

**REVISTA / JOURNAL:** - J Natl Cancer Inst. 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt298](#)

**AUTORES / AUTHORS:** - Ogino S; Liao X; Imamura Y; Yamauchi M; McCleary NJ; Ng K; Niedzwiecki D; Saltz LB; Mayer RJ; Whittom R; Hantel A; Benson AB 3rd; Mowat RB; Spiegelman D; Goldberg RM; Bertagnolli MM; Meyerhardt JA; Fuchs CS

**INSTITUCIÓN / INSTITUTION:** - Affiliations of authors: Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA (SO, XL, YI, MY, NJM, KN, RJM, JAM, CSF); Department of Pathology (SO), Channing Division of Network Medicine, Department of Medicine (DS, CSF), and Department of Surgery (MMB), Brigham and Women's Hospital and Harvard Medical School, Boston, MA (SO); Department of Epidemiology (SO, DS) and Department of Biostatistics (DS), Harvard School of Public Health, Boston, MA; Alliance Statistics and Data Center, Duke University Medical Center, Durham, NC (DN); Memorial Sloan-Kettering Cancer Center, New York, NY (LBS); Hopital du Sacre-Coeur de Montreal, Montreal, Canada (RW); Loyola University Stritch School of Medicine, Maywood, IL (AH); current: Edward Cancer Center, Naperville, IL (AH); Northwestern University, Chicago, IL (ABB); Toledo Community Hospital Oncology Program, Toledo, OH (RBM); Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH (RMG).

**RESUMEN / SUMMARY:** - BACKGROUND: Somatic mutations in PIK3CA (phosphatidylinositol-4,5-bisphosphonate 3-kinase [PI3K], catalytic subunit alpha gene) activate the PI3K-AKT signaling pathway and contribute to pathogenesis of various malignancies, including colorectal cancer. METHODS: We examined associations of PIK3CA oncogene mutation with relapse, survival, and treatment efficacy in 627 stage III colon carcinoma case subjects within a randomized adjuvant chemotherapy trial (5-fluorouracil and leucovorin [FU/LV] vs irinotecan [CPT11], fluorouracil and leucovorin [IFL]; Cancer and Leukemia Group B 89803 [Alliance]). We detected PIK3CA mutation in exons 9 and 20 by polymerase chain reaction and pyrosequencing. Cox proportional hazards model was used to assess prognostic and predictive role of PIK3CA mutation, adjusting for clinical features and status of routine standard molecular pathology features, including KRAS and BRAF mutations and microsatellite instability (mismatch repair deficiency). All statistical tests were two-sided. RESULTS: Compared with PIK3CA wild-type cases, overall status of PIK3CA mutation positivity or the presence of PIK3CA mutation in either exon 9 or 20 alone was not statistically significantly associated with recurrence-free, disease-free, or overall survival (log-rank  $P > .70$ ;  $P > .40$  in multivariable regression models). There was no statistically significant interaction between PIK3CA and KRAS (or BRAF) mutation status in survival analysis ( $P$  interaction  $> .18$ ). PIK3CA mutation status did not appear to predict better or worse response to IFL therapy compared with FU/LV therapy ( $P$  interaction  $> .16$ ). CONCLUSIONS: Overall tumor PIK3CA mutation status is not associated with stage III colon cancer prognosis. PIK3CA mutation does not appear to serve as a predictive tumor molecular biomarker for response to irinotecan-based adjuvant chemotherapy.

[8]

**TÍTULO / TITLE:** - Core binding factor acute myeloid leukemia in pediatric patients enrolled in the AIEOP AML 2002/01 trial: screening and prognostic impact of c-KIT mutations.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Nov 14. doi: 10.1038/leu.2013.339.

●● [Enlace al texto completo \(gratis o de pago\) 1038/leu.2013.339](#)

**AUTORES / AUTHORS:** - Manara E; Bisio V; Masetti R; Beqiri V; Rondelli R; Menna G; Micalizzi C; Santoro N; Locatelli F; Basso G; Pigazzi M

**INSTITUCIÓN / INSTITUTION:** - Clinica di Oncoematologia Pediatrica, Universita degli Studi di Padova, Padova, Italy;

[9]

**TÍTULO / TITLE:** - Prediction of overall survival or progression free survival by disease control rate at week 8 is independent of ethnicity: Western versus Chinese patients with first-line non-small cell lung cancer treated with chemotherapy with or without bevacizumab.

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

**REVISTA / JOURNAL:** - J Clin Pharmacol. 2013 Oct 3. doi: 10.1002/jcph.191.

●● [Enlace al texto completo \(gratis o de pago\) 1002/jcph.191](#)

**AUTORES / AUTHORS:** - Claret L; Gupta M; Han K; Joshi A; Sarapa N; He J; Powell B; Bruno R

**INSTITUCIÓN / INSTITUTION:** - Pharsight Consulting Services, Pharsight, A Certara Company, Marseille, France.

**RESUMEN / SUMMARY:** - Categorizations of best response observed at week 8 (between week 3 and 14) of first-line treatment in two studies of bevacizumab plus chemotherapy in Western (878 patients) and Chinese (198 patients) patients with non-small cell lung cancer were assessed together with baseline prognostic factors in multivariate parametric models to predict overall survival (OS) and progression free survival (PFS). Predictive performances of the models were assessed by simulating multiple replicates of the studies. Disease control rate (DCR) was the best response categorization to predict OS and PFS. In the OS model, DCR fully captured bevacizumab effect. For PFS, DCR did not fully capture bevacizumab treatment effect. The models adequately predicted OS and PFS distributions in each arm as well as bevacizumab hazard ratio (HR) for OS and PFS, for example, in Western patients (model prediction [95% prediction interval]: 0.84 [0.71-0.98] vs. observed: 0.77 for OS and 0.59 [0.49-0.72] vs. observed: 0.58 for PFS). Covariates in the models captured endpoint differences seen in Chinese patients. There was no impact of Chinese ethnicity on the DCR relationship to OS or PFS. DCR predicted OS benefit with bevacizumab in first-line NSCLC patients. Western data can be used to inform design of studies in Chinese patients.

[10]

**TÍTULO / TITLE:** - Phase II trial of erlotinib in patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations: additive analysis of pharmacokinetics.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Oct 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2307-6](#)

**AUTORES / AUTHORS:** - Motoshima K; Nakamura Y; Sano K; Ikegami Y; Ikeda T; Mizoguchi K; Takemoto S; Fukuda M; Nagashima S; Iida T; Tsukamoto K; Kohno S

**INSTITUCIÓN / INSTITUTION:** - Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan.

**RESUMEN / SUMMARY:** - **BACKGROUND:** We conducted a phase II trial of erlotinib in patients with advanced non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations and evaluated the relationship between plasma concentration and efficacy of erlotinib. **METHODS:** Patients who were previously treated but naive to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), with advanced NSCLC harboring EGFR mutations, were enrolled. Erlotinib was given at 150 mg once daily until disease progression. The primary end point was objective response rate (ORR). Plasma trough levels of erlotinib were measured on Days 2 (D2) and 8 (D8) by high-performance liquid chromatography. **RESULTS:** In total, 29 patients were enrolled from September 2008 to January 2011. ORR was 61.5 % (95 % confidence interval [CI] 40.57-79.8) of 26 assessable patients. The median progression-free survival (PFS) and overall survival (OS) were 6.3 months and 16.9 months, respectively. Skin rash was observed in 24 patients, mostly at grade 1 or 2. Grade 2 pneumonitis was observed in one patient. We

collected blood samples from 16 patients. The median PFS of the high and low D8/D2 ratio group was 11.2 months and 5.7 months, respectively ( $p = 0.044$ , hazard ratio = 0.301, 95 % CI 0.094-0.968). CONCLUSION: Erlotinib showed an ORR comparable to that seen in previous studies for patients with NSCLC harboring EGFR mutations, although response, the primary end point, did not reach the predetermined threshold level. The D8/D2 ratio of erlotinib plasma trough levels might be a predictive factor for PFS.

[11]

**TÍTULO / TITLE:** - Cancer-drug discovery and cardiovascular surveillance.

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

**REVISTA / JOURNAL:** - N Engl J Med. 2013 Nov 7;369(19):1779-81. doi: 10.1056/NEJMp1313140. Epub 2013 Nov 1.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMp1313140](#)

**AUTORES / AUTHORS:** - Groarke JD; Cheng S; Moslehi J

**INSTITUCIÓN / INSTITUTION:** - From the Cardio-Oncology Program at the Dana-Farber Cancer Institute (J.D.G., J.M.) and the Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital (J.D.G., S.C., J.M.); and Harvard Medical School (J.D.G., S.C., J.M.) - all in Boston.

[12]

**TÍTULO / TITLE:** - Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Nov 12. doi: 10.1002/cncr.28476.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28476](#)

**AUTORES / AUTHORS:** - George S; Feng Y; Manola J; Nucci MR; Butrynski JE; Morgan JA; Ramaiya N; Quek R; Penson RT; Wagner AJ; Harmon D; Demetri GD; Krasner C

**INSTITUCIÓN / INSTITUTION:** - Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

**RESUMEN / SUMMARY:** - BACKGROUND: Advanced uterine leiomyosarcoma (ULMS) is an incurable disease. A significant percentage of cases of ULMS express estrogen and/or progesterone receptors (ER and/or PR). To the authors' knowledge, the role of estrogen suppression in disease management is not known. METHODS: The authors performed a single-arm phase 2 study of the aromatase inhibitor letrozole at a dose of 2.5 mg daily in patients with unresectable ULMS with ER and/or PR expression confirmed by immunohistochemistry. Tumor assessments were performed at baseline, 6 weeks, 12 weeks, and every 8 weeks thereafter. Toxicity was monitored throughout treatment. The primary endpoint was the progression-free survival at 12 weeks. RESULTS: A total of 27 patients was accrued, with a median of 2 prior treatment regimens (range, 0-9 treatment regimens). The median duration of protocol treatment was 2.2 months (range, 0.4 months-9.9 months). The 12-week progression-free survival rate was 50% (90% confidence interval, 30%-67%). The best response was stable disease in 14 patients (54%; 90% CI, 36%-71%). Three patients, all of whom had tumors expressing ER and PR in > 90% of tumor cells, continued to receive

letrozole for > 24 weeks. The most common reason for treatment discontinuation was disease progression (85%). Letrozole was found to be well tolerated. CONCLUSIONS: Letrozole met protocol-defined criteria as an agent with activity in patients with advanced ULMS. Patients with the longest progression-free survival rate were those whose tumors strongly and diffusely expressed ER and PR. Cancer 2013. © 2013 American Cancer Society.

[13]

**TÍTULO / TITLE:** - HER2-positive patients receiving trastuzumab treatment have a comparable prognosis with HER2-negative advanced gastric cancer patients: A prospective cohort observation.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 23. doi: 10.1002/ijc.28559.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28559](#)

**AUTORES / AUTHORS:** - Qiu MZ; Li Q; Wang ZQ; Liu TS; Liu Q; Wei XL; Jin Y; Wang DS; Ren C; Bai L; Zhang DS; Wang FH; Li YH; Xu RH

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China.

**RESUMEN / SUMMARY:** - The monoclonal antibody trastuzumab has brought survival benefit to patients with advanced gastric cancer (AGC) that have human epidermal growth factor receptor 2 (HER2) over expression or amplification. This study was designed to compare the clinical outcomes of HER2-negative and HER2-positive AGC patients with or without trastuzumab treatment. There were three groups of patients enrolled for analysis. Group A was 51 HER2-positive AGC patients treated with trastuzumab and chemotherapy; group B was a matched control group of 47 HER2-positive patients who received chemotherapy only; group C was a matched group of 251 HER2-negative patients who received chemotherapy. All the patients were enrolled at Sun Yat-sen University Cancer Center or Zhongshan Hospital, Fudan University between January 2010 and December 2012. The primary endpoint was overall survival (OS). The Kaplan-Meier method and log-rank test were used for survival analysis. The median duration of follow-up was 13.5 months (range 5-18.6 months). The median OS of these three groups of patients was 14.8 months, 11.3 months and 14.4 months respectively ( $p < 0.001$ ). The survival difference between group A and B was significant,  $p < 0.001$ . Similarly, there was significant difference between group B and C,  $p < 0.001$ . Moreover the survival between group A and C was comparable,  $p = 0.281$ . The median progression-free survival for these three groups was 7.4, 6.0 and 7.2 months. Multivariate analysis confirmed that trastuzumab treatment was an independent prognostic factor in group A and B patients ( $p = 0.017$ ). HER2 positive was an independent adverse prognostic factor in group B and C patients ( $p = 0.013$ ).

[14]

**TÍTULO / TITLE:** - Phase II trial to assess the safety and efficacy of clofarabine in combination with low-dose cytarabine in elderly patients with acute myeloid leukemia.

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

**REVISTA / JOURNAL:** - Ann Hematol. 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1914-y](http://1007/s00277-013-1914-y)

**AUTORES / AUTHORS:** - Martínez-Cuadrón D; Montesinos P; Oriol A; Salamero O; Vidriales B; Bergua J; Herrera P; Vives S; Sanz J; Carpio C; Rodríguez-Veiga R; Moscardo F; Sanz MA

**INSTITUCIÓN / INSTITUTION:** - Hematology Department, Hospital Universitari i Politècnic La Fe, Bulevar Sur s/n, 46026, Valencia, España.

**RESUMEN / SUMMARY:** - Previous studies have shown that clofarabine plus low-dose cytarabine (LDAC) could induce roughly 60 % of complete remissions (CR) with acceptable toxicity and induction mortality in elderly acute myeloid leukemia (AML) patients not suitable for intensive chemotherapy. The Programa Español de Tratamientos en Hematología group conducted a trial for patients diagnosed with untreated AML aged 60 years and older, using the combination of clofarabine (20 mg/m<sup>2</sup> x 5 days) plus low-dose cytarabine (20 mg/m<sup>2</sup> x 14 days). The protocol was flexible regarding the use of antifungal and antibacterial prophylaxis, and outpatient induction therapy was allowed. Although the planned recruitment goal was 75 patients, only 11 patients were enrolled (median age, 74 years) after observing high toxicity and unacceptable mortality (46 and 73 % at 4 and 8 weeks, respectively). The response assessment showed three CR (27 %), three resistant diseases (27 %), and five induction deaths (46 %). Induction was administered in an outpatient modality in five patients, while antifungal and antibacterial prophylaxis was not given in seven and five patients, respectively. In our context, induction therapy with the combination of clofarabine (20 mg/m<sup>2</sup>) plus LDAC was associated with high toxicity and unacceptable mortality in elderly AML patients, leading to the early interruption of the trial. Tight patients' clinical monitoring, follow-up, and intensive supportive care seem crucial to achieve at least acceptable clinical outcomes in elderly AML patients receiving clofarabine plus LDAC. This trial is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as no. NCT01193400.

[15]

**TÍTULO / TITLE:** - Efficacy of oral cytarabine ocfosfate and etoposide in the treatment of elderly patients with higher-risk myelodysplastic syndromes compared to that in elderly acute myeloid leukemia patients.

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

**REVISTA / JOURNAL:** - Chemotherapy. 2013;59(2):152-8. doi: 10.1159/000351114. Epub 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [1159/000351114](http://1159/000351114)

**AUTORES / AUTHORS:** - Horikoshi A; Iriyama N; Hirabayashi Y; Kodaira H; Matsukawa Y; Uchino Y; Takahashi H; Hatta Y; Takeuchi J; Kobayashi S; Miura K

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Rheumatology, Department of Internal Medicine, Nihon University Itabashi Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: Elderly acute myeloid leukemia (AML) patients and patients with higher-risk myelodysplastic syndromes (MDS) have a much poorer prognosis than younger patients despite intensive chemotherapy. METHODS: Ten patients with higher-risk MDS and 12 patients with AML over 65 years of age were enrolled into this study and received oral induction therapy with cytarabine ocfosfate and etoposide. RESULTS: The therapy response rates were 60% in the MDS group

and 41.7% in the AML group. The difference in overall survival among MDS and AML patients was not statistically significant. The difference in the median survival times of the responsive and nonresponsive groups, which included MDS and AML patients, was statistically significant (790 and 174 days, respectively). CONCLUSIONS: Based on a comparison of the data of this therapy in elderly higher-risk MDS patients versus elderly AML patients, we conclude that this therapy is well tolerated and can be cost-effective and useful for higher-risk MDS in elderly patients.

[16]

**TÍTULO / TITLE:** - TRAIL receptor agonist conatumumab with modified FOLFOX6 plus bevacizumab for first-line treatment of metastatic colorectal cancer: A randomized phase 1b/2 trial.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Oct 1. doi: 10.1002/cncr.28353.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28353](#)

**AUTORES / AUTHORS:** - Fuchs CS; Fakih M; Schwartzberg L; Cohn AL; Yee L; Dreisbach L; Kozloff MF; Hei YJ; Galimi F; Pan Y; Haddad V; Hsu CP; Sabin A; Saltz L

**INSTITUCIÓN / INSTITUTION:** - Dana-Farber Cancer Institute, Boston, Massachusetts.

**RESUMEN / SUMMARY:** - BACKGROUND: In patients with previously untreated metastatic colorectal cancer (mCRC), we conducted a phase 1b/randomized phase 2 trial to define the safety, tolerability, and efficacy of mFOLFOX6 plus bevacizumab (mFOLFOX6/bev) with conatumumab, an investigational, fully human monoclonal IgG1 antibody that specifically activates death receptor 5 (DR5). METHODS: Twelve patients were enrolled in a phase 1b open-label dose-escalation trial of conatumumab with mFOLFOX6/bev; thereafter, 190 patients were randomized 1:1:1 to receive mFOLFOX6/bev in combination with 2 mg/kg conatumumab, 10 mg/kg conatumumab, or placebo. Therapy cycles were repeated every 2 weeks until disease progression or the occurrence of unacceptable toxicity. RESULTS: In phase 1b, conatumumab with mFOLFOX6/bev was tolerated without apparent added toxicity over mFOLFOX6/bev alone. In phase 2, conatumumab with mFOLFOX6/bev did not confer a benefit in progression-free survival when compared with placebo with mFOLFOX6/bev. Toxicity was similar in all treatment arms. Following treatment, similar increases in circulating caspase-3 levels were observed in all arms. CONCLUSIONS: Conatumumab with mFOLFOX6/bev did not offer improved efficacy over the same chemotherapy with placebo in first-line treatment of patients with mCRC. These data do not support further development of conatumumab in advanced CRC. Cancer 2013. © 2013 American Cancer Society.

[17]

**TÍTULO / TITLE:** - Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy.

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

**REVISTA / JOURNAL:** - J Natl Cancer Inst. 2013 Nov 20;105(22):1729-37. doi: 10.1093/jnci/djt280. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt280](#)

**AUTORES / AUTHORS:** - Halabi S; Lin CY; Small EJ; Armstrong AJ; Kaplan EB; Petrylak D; Sternberg CN; Shen L; Oudard S; de Bono J; Sartor O

**INSTITUCIÓN / INSTITUTION:** - Affiliations of authors: Department of Biostatistics and Bioinformatics, (SH, C-YL, EK), and Alliance Statistics and Data Center (SH), Duke University, Durham, NC; Departments of Medicine and Urology, University of California-San Francisco, San Francisco, CA (EJS); Division of Medical Oncology, Duke Prostate Center and the Duke Cancer Institute, Durham, NC (AJA); Departments of Medical Oncology and Urology, Yale University Cancer Center, New Haven, CT (DP); Department of Medical Oncology, San Camillo and Forlanini Hospital, Rome, Italy (CNS); Sanofi, Malvern, PA (LS); Department of Medical Oncology, Georges Pompidou European Hospital, Paris, France (SO); Department of Clinical Studies, Royal Marsden Hospital and Institute of Cancer Research, Surrey, United Kingdom (JdB); Urology Department, Tulane Cancer Center, New Orleans, LA (OS).

**RESUMEN / SUMMARY:** - **BACKGROUND:** Several prognostic models for overall survival (OS) have been developed and validated in men with metastatic castration-resistant prostate cancer (mCRPC) who receive first-line chemotherapy. We sought to develop and validate a prognostic model to predict OS in men who had progressed after first-line chemotherapy and were selected to receive second-line chemotherapy. **METHODS:** Data from a phase III trial in men with mCRPC who had developed progressive disease after first-line chemotherapy (TROPIC trial) were used. The TROPIC was randomly split into training (n = 507) and testing (n = 248) sets. Another dataset consisting of 488 men previously treated with docetaxel (SPARC trial) was used for external validation. Adaptive least absolute shrinkage and selection operator selected nine prognostic factors of OS. A prognostic score was computed from the regression coefficients. The model was assessed on the testing and validation sets for its predictive accuracy using the time-dependent area under the curve (tAUC). **RESULTS:** The nine prognostic variables in the final model were Eastern Cooperative Oncology Group performance status, time since last docetaxel use, measurable disease, presence of visceral disease, pain, duration of hormonal use, hemoglobin, prostate specific antigen, and alkaline phosphatase. The tAUCs for this model were 0.73 (95% confidence interval [CI] = 0.72 to 0.74) and 0.70 (95% CI = 0.68 to 0.72) for the testing and validation sets, respectively. **CONCLUSIONS:** A prognostic model of OS in the postdocetaxel, second-line chemotherapy, mCRPC setting was developed and externally validated. This model incorporates novel prognostic factors and can be used to provide predicted probabilities for individual patients and to select patients to participate in clinical trials on the basis of their prognosis. Prospective validation is needed.

[18]

**TÍTULO / TITLE:** - Validation of the 12-Gene Colon Cancer Recurrence Score in NSABP C-07 As a Predictor of Recurrence in Patients With Stage II and III Colon Cancer Treated With Fluorouracil and Leucovorin (FU/LV) and FU/LV Plus Oxaliplatin.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 12.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2012.47.3116](#)

**AUTORES / AUTHORS:** - Yothers G; O'Connell MJ; Lee M; Lopatin M; Clark-Langone KM; Millward C; Paik S; Sharif S; Shak S; Wolmark N

**INSTITUCIÓN / INSTITUTION:** - Greg Yothers, Michael J. O'Connell, Soonmyung Paik, Saima Sharif, and Norman Wolmark, National Surgical Adjuvant Breast and Bowel Project (NSABP) Operations and Biostatistical Centers; Greg Yothers, University of Pittsburgh Graduate School of Public Health; Saima Sharif and Norman Wolmark, Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA; Mark Lee, Margarita Lopatin, Kim M. Clark-Langone, and Steven Shak, Genomic Health, Redwood City, CA.

**RESUMEN / SUMMARY:** - **PURPOSE:** Accurate assessments of recurrence risk and absolute treatment benefit are needed to inform colon cancer adjuvant therapy. The 12-gene Recurrence Score assay has been validated in patients with stage II colon cancer from the Cancer and Leukemia Group B 9581 and Quick and Simple and Reliable (QUASAR) trials. We conducted an independent, prospectively designed clinical validation study of Recurrence Score, with prespecified end points and analysis plan, in archival specimens from patients with stage II and III colon cancer randomly assigned to fluorouracil (FU) or FU plus oxaliplatin in National Surgical Adjuvant Breast and Bowel Project C-07. **METHODS:** Recurrence Score was assessed in 892 fixed, paraffin-embedded tumor specimens (randomly selected 50% of patients with tissue). Data were analyzed by Cox regression adjusting for stage and treatment. **RESULTS:** Continuous Recurrence Score predicted recurrence (hazard ratio for a 25-unit increase in score, 1.96; 95% CI, 1.50 to 2.55;  $P < .001$ ), as well as disease-free and overall survival (both  $P < .001$ ). Recurrence Score predicted recurrence risk ( $P = .001$ ) after adjustment for stage, mismatch repair, nodes examined, grade, and treatment. Recurrence Score did not have significant interaction with stage ( $P = .90$ ) or age ( $P = .76$ ). Relative benefit of oxaliplatin was similar across the range of Recurrence Score (interaction  $P = .48$ ); accordingly, absolute benefit of oxaliplatin increased with higher scores, most notably in patients with stage II and IIIA/B disease. **CONCLUSION:** The 12-gene Recurrence Score predicts recurrence risk in stage II and stage III colon cancer and provides additional information beyond conventional clinical and pathologic factors. Incorporating Recurrence Score into the clinical context may better inform adjuvant therapy decisions in stage III as well as stage II colon cancer.

[19]

**TÍTULO / TITLE:** - An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era.

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

**REVISTA / JOURNAL:** - Blood. 2013 Nov 21.

●● [Enlace al texto completo \(gratis o de pago\) 1182/blood-2013-09-524108](#)

**AUTORES / AUTHORS:** - Zhou Z; Sehn LH; Rademaker AW; Gordon LI; Lacasce AS; Crosby-Thompson A; Vanderplas A; Zelenetz AD; Abel GA; Rodriguez MA; Nademanee A; Kaminski MS; Czuczman MS; Millenson M; Niland J; Gascoyne RD; Connors JM; Friedberg JW; Winter JN

**INSTITUCIÓN / INSTITUTION:** - Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, United States;

**RESUMEN / SUMMARY:** - The International Prognostic Index (IPI) has been the basis for determining prognosis in patients with aggressive non-Hodgkin lymphoma (NHL) for the past 20 years. Using raw clinical data from the National Comprehensive Cancer Network (NCCN) database collected during the rituximab era, we built an enhanced IPI

with the goal of improving risk stratification. Adults (n=1,650) with de novo diffuse large B-cell lymphoma (DLBCL) diagnosed over a 10-year period at 7 NCCN cancer centers were included. Clinical features were assessed for their prognostic significance, with statistical efforts to further refine the categorization of age and normalized LDH. This new NCCN-IPI identified 5 predictors (age, LDH, sites of involvement, Ann Arbor stage, ECOG performance status) and assigned a maximum of 8 points. Four risk groups were formed: low (0-1), low-intermediate (2-3), high-intermediate (4-5) and high (6-8). Compared to the IPI, the NCCN-IPI better discriminated low and high risk subgroups (5-year overall survival [OS]: 96% vs 33%) than the IPI (5 year OS: 90% vs 54%), respectively. When validated using an independent cohort from the British Columbia Cancer Agency (n=1,138), it also demonstrated enhanced discrimination for both low and high risk patients. The NCCN-IPI is easy to apply and more powerful than the IPI for predicting survival in the rituximab era.

[20]

**TÍTULO / TITLE:** - Prognostic factors for disease-free survival after preoperative chemotherapy followed by curative resection in patients with colorectal cancer harboring hepatic metastasis: a single-institute, retrospective analysis in Asia.

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

**REVISTA / JOURNAL:** - Oncology. 2013;85(5):283-9. doi: 10.1159/000355475. Epub 2013 Nov 6.

●● [Enlace al texto completo \(gratis o de pago\) 1159/000355475](#)

**AUTORES / AUTHORS:** - Yi JH; Kim H; Jung M; Shin SJ; Choi JS; Choi GH; Baik SH; Min BS; Kim NK; Ahn JB

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - Background: Converting chemotherapy followed by surgery is known to be associated with improved clinical outcomes in colorectal cancer (CRC) patients with hepatic metastasis. This study is to investigate the clinicopathological prognostic factors for disease-free survival (DFS) after curative resection of primary and metastatic lesions. Methods: We retrospectively analyzed the medical records of 76 CRC patients who had initially had unresectable hepatic metastasis, which was considered resectable after systemic chemotherapy, and had undergone curative surgery in the period from January 2006 to December 2011. DFS was compared by assessing clinical data including age, sex, staging, number of hepatic lesion(s), size of the largest hepatic lesion and serum carcinoembryonic antigen (CEA) levels. Results: The median age was 57 years and 47 patients were male. The median DFS was 10.4 months. Multivariate Cox regression analysis revealed that age <50 years (HR 2.70, 95% CI 1.43-5.10, p = 0.002) and CEA elevation after curative surgery (HR 2.20, 95% CI 1.11-4.36, p = 0.023) were associated with a shorter DFS. Conclusions: Given that patients <50 years old or with elevated CEA levels after curative surgery demonstrated a short DFS, additional postoperative systemic treatment or active surveillance, at least, should strongly be considered for this group. © 2013 S. Karger AG, Basel.

[21]

**TÍTULO / TITLE:** - Baseline glyceimic parameters predict the hemoglobin A response to DPP-4 inhibitors : Meta-regression analysis of 78 randomized controlled trials with 20,053 patients.

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

**REVISTA / JOURNAL:** - Endocrine. 2013 Nov 20.

●● Enlace al texto completo (gratis o de pago) [1007/s12020-013-0090-0](#)

**AUTORES / AUTHORS:** - Esposito K; Chiodini P; Capuano A; Maiorino MI; Bellastella G; Giugliano D

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical and Experimental Medicine and Surgery, Second University of Naples, Naples, Italy, [katherine.esposito@unina2.it](mailto:katherine.esposito@unina2.it).

**RESUMEN / SUMMARY:** - Ability to predict which patients might benefit more of therapy might facilitate personalization of treatment. The aim of this study was to obtain information about clinical characteristics which might predict the HbA1c response to DPP-4 inhibitors. We conducted an electronic search without restriction for randomized controlled trials (RCTs) involving DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin, and alogliptin). RCTs were included if they lasted at least 12 weeks, reported the effect of DPP-4 inhibitors on HbA1c level, and the number of patients in any arm was >30. We did a meta-regression analysis. Seventy-eight articles were eligible, with 79 arms and 20,503 patients. For all arms, the decrease of HbA1c was -0.74 % (95 % CI -0.80 to -0.67 %), with considerable heterogeneity ( $I^2 = 97 %$ ,  $P < 0.0001$ ): the greatest HbA1c decrease was seen at 52 weeks (8 arms, 3,338 patients, -0.88 %, 95 % CI -1.10 to -0.66 %). In univariate meta-regression analysis, baseline HbA1c explained 22 % of variance of the HbA1c response to treatment, while fasting glucose and type of DPP-4 inhibitor explained an additional 19 and 12 %, respectively; age, duration of treatment, previous therapy, and type of statistical analysis of RCTs were without influence. In the multivariate meta-regression model, baseline HbA1c, fasting glucose, and type of DPP-4 inhibitor explained 61 % of total variance. The HbA1c response to DPP-4 inhibitors can be modulated mainly by baseline HbA1c and fasting glucose levels: a greater absolute reduction of baseline HbA1c is seen in patients with higher baseline HbA1c and lower fasting glucose level.

[22]

**TÍTULO / TITLE:** - Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a rituximab-intensive program.

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

**REVISTA / JOURNAL:** - Blood. 2013 Nov 28;122(23):3759-66. doi: 10.1182/blood-2013-06-507319. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-06-507319](#)

**AUTORES / AUTHORS:** - Ladetto M; Lobetti-Bodoni C; Mantoan B; Ceccarelli M; Boccomini C; Genuardi E; Chiappella A; Baldini L; Rossi G; Pulsoni A; Di Raimondo F; Rigacci L; Pinto A; Galimberti S; Bari A; Rota-Scalabrini D; Ferrari A; Zaja F; Gallamini A; Specchia G; Musto P; Rossi FG; Gamba E; Evangelista A; Vitolo U

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Turin, Turin, Italy;

**RESUMEN / SUMMARY:** - We assessed the prognostic value of minimal residual disease (MRD) within the ML17638 phase 3 trial from the Fondazione Italiana Linfomi, investigating the role of rituximab maintenance in elderly follicular lymphoma (FL)

patients after a brief first-line chemoimmunotherapy. MRD for the bcl-2/IgH translocation was determined on bone marrow cells in a centralized laboratory belonging to the Euro-MRD consortium, using qualitative and quantitative polymerase chain reactions (PCRs). Of 234 enrolled patients, 227 (97%) were screened at diagnosis. A molecular marker (MM) was found in 51%. Patients with an MM were monitored at 8 subsequent times. Of the 675 expected follow-up samples, 83% were analyzed. Conversion to PCR negativity predicted better progression-free survival (PFS) at all post-treatment times (eg, end of therapy: 3-year PFS, 72% vs 39%;  $P < .007$ ). MRD was predictive in both maintenance (83% vs 60%;  $P < .007$ ) and observation (71% vs 50%;  $P < .001$ ) groups. PCR positivity at the end of induction was an independent adverse predictor (hazard ratio, 3.1; 95% confidence interval, 1.36-7.07). MRD is a powerful independent outcome predictor in FL patients who receive rituximab-intensive programs, suggesting a need to investigate its value for decision-making. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as #NCT01144364.

[23]

**TÍTULO / TITLE:** - Expression of KIAA0101 protein is associated with poor survival of esophageal cancer patients and resistance to cisplatin treatment in vitro.

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

**REVISTA / JOURNAL:** - Lab Invest. 2013 Dec;93(12):1276-87. doi: 10.1038/labinvest.2013.124. Epub 2013 Oct 21.

●● Enlace al texto completo (gratis o de pago) [1038/labinvest.2013.124](http://1038/labinvest.2013.124)

**AUTORES / AUTHORS:** - Cheng Y; Li K; Diao D; Zhu K; Shi L; Zhang H; Yuan D; Guo Q; Wu X; Liu D; Dang C

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology, The First Affiliated Hospital, Xi'an Jiaotong University College of Medicine, Xi'an, Shaanxi, China.

**RESUMEN / SUMMARY:** - The KIAA0101 protein is overexpressed in various human cancers, including esophageal cancer (EC). This study assessed the association of KIAA0101 protein with prognosis and resistance to chemotherapy in EC patients and then explored the role of KIAA0101 in EC cells in vitro. A total of 228 EC patients participated in the study. Tissue samples were collected for immunohistochemical analysis of KIAA0101 expression in tumor and normal tissues for association with clinicopathological and survival data. KIAA0101 cDNA or shRNA were transfected into EC cells for assessment of tumor cell viability, sensitivity to cisplatin treatment, and gene expression. Array-based comparative genomic hybridization (aCGH) was used to detect the changed copy-number alterations in cell lines expressing different levels of KIAA0101. Expression of KIAA0101 protein was upregulated in EC tissues, which was associated with pTNM stage, resistance to chemotherapy, tumor recurrence, and poor survival of EC patients. In vitro experiments showed that expression of KIAA0101 enhanced cell proliferation and upregulated cyclins A and B expression, leading to a reduced G1 phase of the cell cycle. KIAA0101 also induced resistance of EC Eca-109 and TE-1 cell lines to cisplatin treatment through a decrease in apoptosis. The aCGH data showed that levels of KIAA0101 expression altered chromosome stability, affecting genes that are associated with cancer progression. In conclusion, upregulated KIAA0101 expression is associated with EC progression, resistance to chemotherapy, and poor survival of the patients.

[24]

**TÍTULO / TITLE:** - Circulating hormones and breast cancer risk in premenopausal women: a randomized trial of low-dose tamoxifen and fenretinide.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov 17.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2768-7](#)

**AUTORES / AUTHORS:** - Johansson H; Bonanni B; Gandini S; Guerrieri-Gonzaga A; Cazzaniga M; Serrano D; Macis D; Puccio A; Sandri MT; Gulisano M; Formelli F; Decensi A

**INSTITUCIÓN / INSTITUTION:** - Division of Cancer Prevention and Genetics, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy, [harriet.johansson@ieo.it](mailto:harriet.johansson@ieo.it).

**RESUMEN / SUMMARY:** - Tamoxifen and fenretinide have been extensively studied and exhibit breast cancer-preventing activity. We aimed to assess their effect on sex hormones, sex hormone binding globulin (SHBG) and retinol, and their association with mammographic density (MD) and breast cancer events. In a double-blind, placebo-controlled trial, premenopausal women at risk for breast cancer were randomized to tamoxifen 5 mg/day, fenretinide, both agents, or placebo for 2 years. We measured MD and circulating concentrations of follicle-stimulating hormone, luteinizing hormone (LH), estradiol, progesterone, testosterone, androstenedione, dehydroepiandrosteronesulfate, prolactin, SHBG, and retinol at baseline and on yearly intervals. The associations with breast cancer events were evaluated through competing risk and Cox regression survival models. Low-dose tamoxifen markedly and enduringly increased SHBG, whereas the increases in testosterone, estradiol, and prolactin and reduction in LH weakened after 1 year. Fenretinide increased testosterone and androstenedione and decreased retinol. MD correlated directly with SHBG and inversely with retinol. After a median follow-up of 12 years, the 10-year cumulative incidence of breast cancer events was 37 % in women with SHBG  $\leq$  59.3 nmol/L, 22 % in women with SHBG between 59.3 and 101 nmol/L, and 19 % in women with SHBG > 101 nmol/L (P = 0.018). The difference among SHBG tertiles remained statistically significant at multivariable analysis: HR = 2.26 (95 % CI 1.04, 4.89) for the lowest versus the highest tertile. We conclude that low-dose tamoxifen or fenretinide exhibits favorable hormonal profiles as single agents, further supporting their administration for prevention of breast cancer in premenopause. Notably, SHBG levels were inversely associated with breast neoplastic events.

[25]

**TÍTULO / TITLE:** - Identification of Target Genes Using Gene Expression Profile of Granulocytes From Chronic Myeloid Leukemia (Cml) Patients Treated With Tyrosine Kinase Inhibitors.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Oct 21.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.855311](#)

**AUTORES / AUTHORS:** - Mascarenhas CD; Ferreira da Cunha A; Brugnerotto AF; Gambero S; de Almeida MH; Carazzolle MF; Pagnano KB; Traina F; Costa FF; de Souza CA

**RESUMEN / SUMMARY:** - Abstract Differential gene expression analysis by suppression subtractive hybridization with correlation to the metabolic pathways involved in chronic myeloid leukemia (CML) may provide a new insight into the pathogenesis of CML. Among the overexpressed genes found in CML at diagnosis are SEPT5, RUNX1, MIER1, KPNA6, and FLT3 while PAN3, TOB1 and ITCH were decreased when compared to healthy volunteers. Some genes were identified and involved in CML for the first time, including the TOB1 which showed a low expression in CML patients during tyrosine kinase inhibitors treatment with no complete cytogenetic response. In agreement, reduced expression of TOB1 was also observed in resistant CML patients compared to responsive patients, this might be related to the deregulation of apoptosis and the signaling pathway leading to resistance. Most of identified genes were related to the regulation of NF-kappaB, AKT, Interferon and IL-4 in healthy cells. The results of this study combined with literature data showed specific gene pathways that might be explored as markers to assess the evolution and prognosis in CML as well as to identify new therapeutic targets.

[26]

**TÍTULO / TITLE:** - Clinical-guide risk prediction of hepatocellular carcinoma development in chronic hepatitis C patients after interferon-based therapy.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 29;109(9):2481-8. doi: 10.1038/bjc.2013.564. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.564](#)

**AUTORES / AUTHORS:** - Chang KC; Wu YY; Hung CH; Lu SN; Lee CM; Chiu KW; Tsai MC; Tseng PL; Huang CM; Cho CL; Chen HH; Hu TH

**INSTITUCIÓN / INSTITUTION:** - Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan.

**RESUMEN / SUMMARY:** - Background: Interferon (IFN)-based therapies could eradicate hepatitis C (HCV) and reduce the risk of hepatocellular carcinoma (HCC). However, HCC could still happen after sustained virological response (SVR). We aimed to develop a simple scoring system to predict the risk of HCC development among HCV patients after antiviral therapies. Methods: From 1999 to 2009, 1879 patients with biopsy-proven HCV infection treated with IFN-based therapies were analyzed. Results: Multivariable analysis showed old age (adjusted HR (aHR)=1.73, 95% CI=1.13-2.65 for aged 60-69 and aHR=2.20, 95% CI=1.43-3.37 for aged >=70), Male gender (aHR=1.74, 95% CI=1.26-2.41), platelet count <150 x 10<sup>9</sup>/l (HR=1.91, 95% CI=1.27-2.86), alpha-fetoprotein >=20 ng ml<sup>-1</sup> (HR=2.23, 95% CI=1.58-3.14), high fibrotic stage (HR=3.32, 95% CI=2.10-5.22), HCV genotype 1b (HR=1.53, 95% CI=1.10-2.14), and non SVR (HR=2.40, 95% CI=1.70-3.38) were independent risk factors for HCC. Regression coefficients were used to build up a risk score and the accuracy was evaluated by using the area under the receiver operating characteristic curve (AUC). Three groups as low-, intermediate-, and high-risk are classified based on the risk scores. One hundred sixty patients (12.78%) in the derivation and 82 patients (13.08%) in the validation cohort developed HCC with AUC of 79.4%, sensitivity of 84.38%, and specificity of 60.66%. In the validation cohort, the 5-year HCC incidence was 1.81%, 12.92%, and 29.95% in low-, intermediate-, and high-risk groups, with

hazard ratios 4.49 in intermediate- and 16.14 in high-risk group respectively. The risk reduction of HCC is greatest in patients with SVR, with a 5-year and 10-year risk reduction of 28.91% and 27.99% respectively. Conclusion: The risk scoring system is accurate in predicting HCC development for HCV patients after antiviral therapies.

[27]

**TÍTULO / TITLE:** - A clinical trial of lovastatin for modification of biomarkers associated with breast cancer risk.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov;142(2):389-98. doi: 10.1007/s10549-013-2739-z. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2739-z](#)

**AUTORES / AUTHORS:** - Vinayak S; Schwartz EJ; Jensen K; Lipson J; Alli E; McPherson L; Fernandez AM; Sharma VB; Staton A; Mills MA; Schackmann EA; Telli ML; Kardashian A; Ford JM; Kurian AW

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA.

**RESUMEN / SUMMARY:** - Pre-clinical and epidemiologic studies provide rationale for evaluating lipophilic statins for breast cancer prevention. We conducted a single-arm, biomarker modulation trial of lovastatin among women with increased risk of breast cancer. Eligibility criteria included a deleterious germline mutation in BRCA1, BRCA2, CDH1, or TP53; lifetime breast cancer risk of  $\geq 20\%$  as estimated by the Claus model; or personal history of estrogen receptor and progesterone receptor-negative breast cancer. Participants received 40 mg of lovastatin orally twice daily for 6 months. We evaluated the following biomarkers before and after lovastatin use: breast duct cytology (primary endpoint), serum lipids, C-reactive protein, insulin-like growth factor-1, IGF binding protein-3, lipid peroxidation, oxidative DNA damage, 3-hydroxy-3-methylglutaryl CoA reductase genotype, and mammographic density. Thirty women were enrolled, and 26 (86.7 %) completed the study. For the primary endpoint of changes in breast duct cytology sampled by random periareolar fine needle aspiration, most participants [57.7 %, 95 % confidence interval (CI) 38.9-74.5 %] showed no change after lovastatin; 19.2 % (CI 8.1-38.3 %) had a favorable change in cytology, 7.7 % (95 % CI 1.0-25.3 %) had an unfavorable change, and 15.4 % (95 % CI 5.5-34.2 %) had equivocal results due to acellular specimens, usually after lovastatin. No significant changes were observed in secondary biomarker endpoints. The study was generally well-tolerated: 4 (13.3 %) participants did not complete the study, and one (3.8 %) required a dose reduction. This trial was technically feasible, but demonstrated no significant biomarker modulation; contributing factors may include insufficient sample size, drug dose and/or duration. The results are inconclusive and do not exclude a favorable effect on breast cancer risk.

[28]

**TÍTULO / TITLE:** - Low CHD5 expression activates the DNA damage response and predicts poor outcome in patients undergoing adjuvant therapy for resected pancreatic cancer.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Nov 25. doi: 10.1038/onc.2013.488.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.488](https://doi.org/10.1038/onc.2013.488)

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

**RESUMEN / SUMMARY:** - The DNA damage response (DDR) promotes genome integrity and serves as a cancer barrier in precancerous lesions but paradoxically may promote cancer survival. Genes that activate the DDR when dysregulated could function as useful biomarkers for outcome in cancer patients. Using a siRNA screen in human pancreatic cancer cells, we identified the CHD5 tumor suppressor as a gene, which, when silenced, activates the DDR. We evaluated the relationship of CHD5 expression with DDR activation in human pancreatic cancer cells and the association of CHD5 expression in 80 patients with resected pancreatic adenocarcinoma (PAC) by immunohistochemical analysis with clinical outcome. CHD5 depletion and low CHD5 expression in human pancreatic cancer cells lead to increased H2AX-Ser139 and CHK2-Thr68 phosphorylation and accumulation into nuclear foci. On Kaplan-Meier log-rank survival analysis, patients with low CHD5 expression had a median recurrence-free survival (RFS) of 5.3 vs 15.4 months for patients with high CHD5 expression (P=0.03). In 59 patients receiving adjuvant chemotherapy, low CHD5 expression was associated with decreased RFS (4.5 vs 16.3 months; P=0.001) and overall survival (OS) (7.2 vs 21.6 months; P=0.003). On multivariate Cox regression analysis, low CHD5 expression remained associated with worse OS (HR: 3.187 (95% CI: 1.49-6.81); P=0.003) in patients undergoing adjuvant chemotherapy. Thus, low CHD5 expression activates the DDR and predicts for worse OS in patients with resected PAC receiving adjuvant chemotherapy. Our findings support a model in which dysregulated expression of tumor suppressor genes that induce DDR activation can be utilized as biomarkers for poor outcome. Oncogene advance online publication, 25 November 2013; doi:10.1038/onc.2013.488.

[29]

**TÍTULO / TITLE:** - A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC).

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

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

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2339-y](https://doi.org/10.1007/s00280-013-2339-y)

**AUTORES / AUTHORS:** - Molina AM; Hutson TE; Larkin J; Gold AM; Wood K; Carter D; Motzer R; Michaelson MD

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**RESUMEN / SUMMARY:** - PURPOSE: Lenvatinib is an oral multi-targeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRbeta, RET, and KIT. Everolimus is an oral mammalian target of rapamycin inhibitor approved for advanced renal cell carcinoma (RCC). This phase 1b study assessed safety, maximum tolerated dose (MTD), and preliminary antitumor activity of lenvatinib plus everolimus in metastatic

RCC (mRCC) patients. METHODS: Patients with advanced unresectable or mRCC and Eastern Cooperative Oncology Group performance status 0-1 were eligible (number of prior treatments not restricted). Starting dose was lenvatinib 12 mg once daily with everolimus 5 mg once daily administered continuously in 28-day cycles using a conventional 3 + 3 dose-escalation design. At the MTD, additional patients were enrolled in an expansion cohort. RESULTS: Twenty patients (mean 58.4 years) received lenvatinib [12 mg (n = 7); 18 mg (n = 11); 24 mg (n = 2)] plus everolimus 5 mg. MTD was established as once daily lenvatinib 18 mg plus everolimus 5 mg. The most common treatment-related treatment-emergent adverse events (all dosing cohorts) were fatigue 60 % (Grade  $\geq$ 3: 10 %), mucosal inflammation 50 %, proteinuria (Grade  $\geq$ 3: 15 %), diarrhea (Grade  $\geq$ 3: 10 %), vomiting (Grade  $\geq$ 3: 5 %), hypertension, and nausea, each 40 %. In MTD and lowest-dose cohorts (n = 18), best responses of partial response and stable disease were achieved in 6 (33 %) and 9 (50 %) patients, respectively. CONCLUSIONS: Lenvatinib 18 mg combined with everolimus 5 mg was associated with manageable toxicity consistent with individual agents and no new safety signals. Observed activity warrants further evaluation of the combination in advanced RCC patients.

[30]

**TÍTULO / TITLE:** - A Comparative Analysis of Prognostic Factor Models for Follicular Lymphoma Based on a Phase III Trial of CHOP-Rituximab versus CHOP + 131Iodine—Tositumomab.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Dec 1;19(23):6624-32. doi: 10.1158/1078-0432.CCR-13-1120. Epub 2013 Oct 15.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1120](#)

**AUTORES / AUTHORS:** - Press OW; Unger JM; Rimsza LM; Friedberg JW; Leblanc M; Czuczman MS; Kaminski M; Braziel RM; Spier C; Gopal AK; Maloney DG; Cheson BD; Dakhil SR; Miller TP; Fisher RI

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Clinical Research Division; SWOG Statistical Center, Fred Hutchinson Cancer Research Center; Medical Oncology, University of Washington Medical Center, Seattle, Washington; Department of Pathology; Arizona Cancer Center, University of Arizona, Tucson, Arizona; James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester; Roswell Park Cancer Institute, Buffalo, New York; Cancer and Leukemia Group B; University of Michigan, Ann Arbor, Michigan; Department of Pathology, Oregon Health and Science University, Portland, Oregon; Georgetown University Hospital, Washington; Wichita Community Clinical Oncology Program, Wichita, Kansas; and Fox Chase Cancer Center-Temple Health, Temple University, Philadelphia PA.

**RESUMEN / SUMMARY:** - PURPOSE: There is currently no consensus on optimal frontline therapy for patients with follicular lymphoma. We analyzed a phase III randomized intergroup trial comparing six cycles of CHOP-R (cyclophosphamide-Adriamycin-vincristine-prednisone (Oncovin)-rituximab) with six cycles of CHOP followed by iodine-131 tositumomab radioimmunotherapy (RIT) to assess whether any subsets benefited more from one treatment or the other, and to compare three prognostic models. EXPERIMENTAL DESIGN: We conducted univariate and

multivariate Cox regression analyses of 532 patients enrolled on this trial and compared the prognostic value of the FLIPI (follicular lymphoma international prognostic index), FLIPI2, and LDH + beta2M (lactate dehydrogenase + beta2-microglobulin) models. RESULTS: Outcomes were excellent, but not statistically different between the two study arms [5-year progression-free survival (PFS) of 60% with CHOP-R and 66% with CHOP-RIT (P = 0.11); 5-year overall survival (OS) of 92% with CHOP-R and 86% with CHOP-RIT (P = 0.08); overall response rate of 84% for both arms]. The only factor found to potentially predict the impact of treatment was serum beta2M; among patients with normal beta2M, CHOP-RIT patients had better PFS compared with CHOP-R patients, whereas among patients with high serum beta2M, PFS by arm was similar (interaction P value = 0.02). CONCLUSIONS: All three prognostic models (FLIPI, FLIPI2, and LDH + beta2M) predicted both PFS and OS well, though the LDH + beta2M model is easiest to apply and identified an especially poor risk subset. In an exploratory analysis using the latter model, there was a statistically significant trend suggesting that low-risk patients had superior observed PFS if treated with CHOP-RIT, whereas high-risk patients had a better PFS with CHOP-R. Clin Cancer Res; 19(23); 6624-32. ©2013 AACR.

[31]

**TÍTULO / TITLE:** - Pathological response on surgical samples is an independent prognostic variable for patients with Stage Ib2-IIb cervical cancer treated with neoadjuvant chemotherapy and radical hysterectomy: An Italian multicenter retrospective study (CTF Study).

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

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Dec;131(3):640-4. doi: 10.1016/j.ygyno.2013.09.029. Epub 2013 Oct 3.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ygyno.2013.09.029](#)

**AUTORES / AUTHORS:** - Gadducci A; Sartori E; Maggino T; Zola P; Cosio S; Zizioli V; Lapresa M; Piovano E; Landoni F

**INSTITUCIÓN / INSTITUTION:** - Department of Procreative Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy.

**RESUMEN / SUMMARY:** - OBJECTIVES: The purpose of this retrospective multicenter study was to correlate patterns of recurrences and clinical outcome of cervical cancer patients who underwent neoadjuvant chemotherapy [NACT] to surgery. METHODS: This study was conducted on 333 patients with FIGO stage Ib2-IIb cervical cancer who underwent NACT to surgery with pelvic lymphadenectomy. The median follow-up was 66.5months (range, 8-212months). Overall optimal response rate was the sum of complete and optimal partial response rates. RESULTS: An overall optimal response was obtained in 64 patients (19.2%). As for the 220 sub-optimal responders (66.1%), 127 patients had negative nodes and negative parametria and/or surgical margins, 75 patients had positive nodes with positive or negative parametria and/or surgical margins, and 18 patients had positive parametria and/or surgical margins with negative nodes. At the time of the present analysis, 79 (23.7%) of the 333 patients had a recurrence after a median time of 14.9months (range, 4.5-123months). Recurrent disease was pelvic in 50 (63.3%), extra-pelvic in 22 (27.9%), and both in 7 (8.8%). On multivariate analysis, pathological response to NACT was an independent prognostic variable for recurrence-free and overall survival. Patients who did not achieve an

overall optimal response had a 2.757-fold higher risk of recurrence and a 5.413-fold higher risk of death than those who obtained an overall optimal response.

CONCLUSIONS: Results appear to suggest that the chemo-surgical approach is an effective therapeutic option for patients with stage Ib2-IIb cervical cancer and that pathological response to NACT is the strongest prognostic factor for the outcome.

[32]

**TÍTULO / TITLE:** - A population-based review of the feasibility of platinum-based combination chemotherapy after tyrosine kinase inhibition in EGFR mutation positive non-small cell lung cancer patients with advanced disease.

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

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Oct 19. pii: S0169-5002(13)00451-0. doi: 10.1016/j.lungcan.2013.10.007.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.10.007](#)

**AUTORES / AUTHORS:** - Mariano C; Bosdet I; Karsan A; Ionescu D; Murray N; Laskin JJ; Zhai Y; Melosky B; Sun S; Ho C

**INSTITUCIÓN / INSTITUTION:** - British Columbia Cancer Agency, Department of Medical Oncology, 600 West 10<sup>th</sup> Avenue, Vancouver, BC, Canada V5Z 4E6.

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**RESUMEN / SUMMARY:** - INTRODUCTION: The IPASS trial demonstrated superior progression free survival for Asian, light/never smoking, advanced, pulmonary adenocarcinoma patients treated with first-line gefitinib compared to carboplatin/paclitaxel, of which 59% of those tested were epidermal growth factor receptor (EGFR) mutation positive. In IPASS 39% of gefitinib treated patients went on to receive platin based polychemotherapy. We hypothesized that in a population-based setting fewer patients receive second-line platin based chemotherapy than those enrolled in a clinical trial. METHODS: The Iressa Alliance program provided standardized EGFR mutation testing and appropriate access to gefitinib to all patients in British Columbia with advanced, non squamous non small cell lung cancer (NSCLC). We retrospectively analyzed clinical, pathologic data and outcomes for all patients tested in this program between March 2010 and June 2011. RESULTS: A total of 548 patients were referred for testing and 22% of patients were mutation positive. Baseline characteristics of mutation negative and mutation positive; median age 67/65, male 41%/31%, Asian 15%/51%, never smoker 21%/58%, stage IV 80%/91%. Median overall survival was 12 months in mutation negative patients and not yet reached in mutation positive ( $p < 0.0001$ ). In mutation positive patients 5% of patients had a complete response, 46% partial response, 34% stable disease, 6% progressive disease. Twenty percent of patients continued on gefitinib after radiographic progression and clinical stability. Sixty-one gefitinib treated patients progressed at the time of analysis; 10% of patients received further gefitinib only, 38% platinum based doublet, 8% other chemotherapy and 44% no further treatment. Performance status most strongly predicted for delivery of second line chemotherapy. CONCLUSIONS: This North American population based study shows similar efficacy of gefitinib in mutation positive patients compared to the IPASS trial. Contrary to our hypothesis, delivery of second line chemotherapy was feasible in a significant proportion of gefitinib treated patients.

[33]

**TÍTULO / TITLE:** - Brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: An European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group randomised phase II and pharmacogenetic study.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Nov 8. pii: S0959-8049(13)00902-7. doi: 10.1016/j.ejca.2013.10.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.10.002](#)

**AUTORES / AUTHORS:** - Gelderblom H; Blay JY; Seddon BM; Leahy M; Ray-Coquard I; Sleijfer S; Kerst JM; Rutkowski P; Bauer S; Ouali M; Marreaud S; van der Straaten RJ; Guchelaar HJ; Weitman SD; Hogendoorn PC; Hohenberger P

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands. Electronic address: [a.j.gelderblom@lumc.nl](mailto:a.j.gelderblom@lumc.nl).

**RESUMEN / SUMMARY:** - AIM: Brostallicin is a DNA minor groove binder that has shown activity in patients with soft tissue sarcoma (STS) failing first-line therapy. The present study assessed the safety and efficacy of first-line brostallicin in patients with advanced or metastatic STS>60years or not fit enough to receive combination chemotherapy. A prospective explorative pharmacogenetic analysis was undertaken in parallel. METHODS: Patients were randomised in a 2:1 ratio between IV brostallicin 10mg/m<sup>2</sup> and doxorubicin 75mg/m<sup>2</sup> once every 3weeks for a maximum of six cycles. Disease stabilisation at 26weeks (primary end-point) was considered a 'success'. Further testing of brostallicin was warranted if 35 'successes' were observed in the first 72 eligible patients treated with brostallicin. In addition, patients were genotyped for glutathione S transferase (GST) polymorphisms. RESULTS: One hundred and eighteen patients were included (79 brostallicin and 39 doxorubicin). Brostallicin was well tolerated in comparison to doxorubicin with less grade 3-4 neutropenia (67% versus 95%), grade 2-3 systolic dysfunction (0% versus 11%), alopecia (17% versus 61%) and grade 2-3 mucositis (0% versus 18%). For brostallicin versus doxorubicin, 'successes' were observed in 5/77 versus 10/36, progression free survival at 1year was 6.5% versus 15.6%, objective response rate was 3.9% versus 22.2% and overall survival at 1year was 50.5% versus 57.9%, respectively. Only GSTA1 genotype was significantly associated with success rate of doxorubicin treatment. CONCLUSION: Brostallicin cannot be recommended at this dose and schedule in this patient population as first-line therapy. GSTA1 genotype may be predictive for doxorubicin efficacy but warrants further study.

[34]

**TÍTULO / TITLE:** - Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Nov 12. doi: 10.1002/cncr.28465.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28465](#)

**AUTORES / AUTHORS:** - Welslau M; Dieras V; Sohn JH; Hurvitz SA; Lalla D; Fang L; Althaus B; Guardino E; Miles D

**INSTITUCIÓN / INSTITUTION:** - Medical Office Hematology, Aschaffenburg, Germany.

**RESUMEN / SUMMARY:** - BACKGROUND: This report describes the results of an analysis of patient-reported outcomes from EMILIA (TDM4370g/BO21977), a randomized phase 3 study of the antibody-drug conjugate trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer. METHODS: A secondary endpoint of the EMILIA study was time to symptom worsening (time from randomization to the first documentation of a  $\geq$  5-point decrease from baseline) as measured by the Trial Outcome Index Physical/Functional/Breast (TOI-PFB) subset of the Functional Assessment of Cancer Therapy-Breast questionnaire. Predefined exploratory patient-reported outcome endpoints included proportion of patients with a clinically significant improvement in symptoms (per TOI-PFB) and proportion of patients with diarrhea symptoms (per Diarrhea Assessment Scale). RESULTS: In the T-DM1 arm, 450 of 495 patients had a baseline and  $\geq$  1 postbaseline TOI-PFB score versus 445 of 496 patients in the capecitabine-plus-lapatinib arm. Time to symptom worsening was delayed in the T-DM1 arm versus the capecitabine-plus-lapatinib arm (7.1 months versus 4.6 months, respectively; hazard ratio = 0.796; P = .0121). In the T-DM1 arm, 55.3% of patients developed clinically significant improvement in symptoms from baseline versus 49.4% in the capecitabine-plus-lapatinib arm (P = .0842). Although similar at baseline, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment with capecitabine and lapatinib but remained near baseline levels in the T-DM1 arm. CONCLUSIONS: Together with the EMILIA primary data, these results support the concept that T-DM1 has greater efficacy and tolerability than capecitabine plus lapatinib, which may translate into improvements in health-related quality of life. Cancer 2013. © 2013 American Cancer Society.

[35]

**TÍTULO / TITLE:** - PI3KCA mutation status is of limited prognostic relevance in ER-positive breast cancer patients treated with hormone therapy.

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

**REVISTA / JOURNAL:** - Virchows Arch. 2013 Nov 15.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00428-013-1500-7](#)

**AUTORES / AUTHORS:** - Cuorvo LV; Verderio P; Ciniselli CM; Girlando S; Decarli N; Leonardi E; Ferro A; Caldara A; Triolo R; Eccher C; Cantaloni C; Mauri F; Seckl M; Volante M; Buttitta F; Marchetti A; Silvia Q; Galligioni E; Palma PD; Barbareschi M

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Molecular Pathology, S. Chiara Hospital, Trento, Italy.

**RESUMEN / SUMMARY:** - PI3K/AKT/mTOR pathway alterations are frequent in patients with infiltrating breast cancer (IBC). Their clinical and pathological relevance has been insufficiently documented. We evaluated PI3KCA for mutations and the expression of PTEN, AKT, mTOR and p70S6K by immunohistochemistry in 246 IBC patients treated with hormone therapy (median follow-up, 97 months). A PI3KCA mutation was observed in 50 out of 229 informative cases (21.8 %), PTEN loss in 107 out of 210 (51 %), moderate/high level of expression of AKT in 133 out of 188 (71 %), moderate/high level of expression of mTOR in 173 out of 218 (79 %) and moderate/high level of

expression of p70S6K in 111 out of 192 cases (58 %). PI3KCA mutation was associated with the absence of Her2/neu amplification/overexpression and a low level of MIB1/Ki-67 labelling. The expression of p70S6K was associated with a high level of mTOR immunoreactivity, and high PTEN expression was associated with high AKT expression level. Univariate analysis showed that PI3KCA mutation status was not associated with clinical outcome in the series as a whole or in the node-negative subgroup. However, in the node-positive subgroup, exon 9 PI3KCA mutation was associated with unfavourable overall survival (OS), although its impact on the final model in multivariate analysis seemed to be limited. Of the other markers, only high p70S6K expression was associated with a significantly prolonged OS. PI3KCA mutation status is of limited prognostic relevance in oestrogen receptor-positive breast cancer patients treated with hormone therapy.

[36]

**TÍTULO / TITLE:** - Do baseline Cereblon gene expression and IL6 receptor expression determine the response to thalidomide-dexamethazone treatment in Multiple myeloma patients?

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

**REVISTA / JOURNAL:** - Eur J Haematol. 2013 Oct 1. doi: 10.1111/ejh.12207.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ejh.12207](#)

**AUTORES / AUTHORS:** - Bedewy AM; El-Maghraby SM

**INSTITUCIÓN / INSTITUTION:** - Hematology Department, Medical Research Institute, Alexandria University.

**RESUMEN / SUMMARY:** - Immunomodulatory drugs (IMiDs) are key components of treatment for hematologic malignancies, especially multiple myeloma (MM). Cereblon (CRBN) expression was described to be essential for the activity of Thalidomide. Furthermore, IMiD binding to CRBN is cytotoxic to multiple myeloma cells and absence of CRBN confers IMiDs resistance. Interleukin-6 (IL-6) is a potent pleiotropic cytokine that regulates plasma cell (PC) growth via the IL-6 receptor (IL-6R). IL-6/IL-6R autocrine activity is implicated in the development and progression of cancers including cervical cancer, prostate cancer and multiple myeloma. The aim of the study was to evaluate CRBN and IL-6R expressions and their impact on clinical efficacy of Dexamethasone-Thalidomide therapy in multiple myeloma (MM) patients, in addition to their association with other clinical and prognostic parameters. Forty six newly diagnosed MM patients were enrolled in the study. We measured CRBN expression prior to therapy initiation by real-time polymerase chain reaction in 46 Bone marrow (BM) aspiration samples of patients and controls. In addition, IL-6R expression was evaluated on BM biopsies of patients and controls by immunohistochemistry (IHC). Twenty eight males (60.9%) and 18 females (39.1%) were enrolled. The mean age was 65.11 +/- 7.3 years (range 39-77 years). Median CRBN expression in 46 BM samples of MM patients was significantly higher than in controls ( $p < 0.001$ ). Among established prognostic parameters, international staging system (ISS), serum beta-2-microglobulin (B2M) and serum albumin correlated reversely with CRBN expression. IL6R expression was significantly higher in patients than in controls. IL6R expression was significantly associated with response to treatment ( $p < 0.001$ ), B2M ( $p = 0.032$ ) and ISS ( $p = 0.028$ ). Strong intensity expression was associated with low CRBN expression ( $p = 0.001$ ). In conclusion, CRBN expression may provide a biomarker to

predict response to IMiD in patients with MM and its high expression can serve as a marker of good prognosis. Strong IL-6R expression is associated with poor response to therapy in multiple myeloma patients and can be used as a prognostic marker. This article is protected by copyright. All rights reserved.

[37]

**TÍTULO / TITLE:** - Validation of the MSKCC and Heng Risk Criteria Models for Predicting Survival in Patients with Metastatic Renal Cell Carcinoma Treated with Sunitinib.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Dec;20(13):4397-404. doi: 10.1245/s10434-013-3290-1. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3290-1](#)

**AUTORES / AUTHORS:** - Kwon WA; Cho IC; Yu A; Nam BH; Joung JY; Seo HK; Lee KH; Chung J

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Wonkwang University College of Medicine, Iksan, Republic of Korea.

**RESUMEN / SUMMARY:** - PURPOSE: To validate the Memorial Sloan-Kettering Cancer Center (MSKCC) and Heng models with metastatic renal cell carcinoma treated with sunitinib, and to investigate prognostic factors in these patients. METHODS: This study included 106 patients with metastatic renal cell carcinoma who were treated with sunitinib from April 2007 to July 2012 including 35 patients who received systemic treatment before sunitinib and 71 that were naive to systemic treatment. Patients were evaluated using the MSKCC and Heng models, and the significance of several prognostic factors were evaluated. RESULTS: The application of the MSKCC and Heng risk criteria resulted in stratification into 3 groups (favorable, intermediate, and poor risk) with distinctly different overall survival (OS) curves ( $P < 0.001$  and  $P < 0.001$ , respectively), for the pretreated patients ( $P < 0.001$  and  $P < 0.001$ , respectively). The Heng model had slightly better discriminatory ability (chi (2) = 30.82, Harrell's C = 0.6895) than the MSKCC model (chi (2) = 25.13, Harrell's C = 0.6532). Multivariate analysis revealed that the absence of nephrectomy and no hypertension at baseline, along with elevated C-reactive protein levels, were independent risk factors for poorer OS. CONCLUSIONS: The MSKCC and Heng model were both valid models for predicting OS. The no nephrectomy, no hypertension at baseline, and high C-reactive protein levels were independently associated with poorer OS.

[38]

**TÍTULO / TITLE:** - Do Angiotensin-converting enzyme inhibitors reduce the risk of symptomatic radiation pneumonitis in patients with non-small cell lung cancer after definitive radiation therapy? Analysis of a single-institution database.

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

**REVISTA / JOURNAL:** - Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):1071-7. doi: 10.1016/j.ijrobp.2013.08.033. Epub 2013 Oct 22.

●● Enlace al texto completo (gratis o de pago) [1016/j.ijrobp.2013.08.033](#)

**AUTORES / AUTHORS:** - Wang H; Liao Z; Zhuang Y; Xu T; Nguyen QN; Levy LB; O'Reilly M; Gold KA; Gomez DR

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong Province, P.R. of China.

**RESUMEN / SUMMARY:** - PURPOSE: Preclinical studies have suggested that angiotensin-converting enzyme inhibitors (ACEIs) can mitigate radiation-induced lung injury. We sought here to investigate possible associations between ACEI use and the risk of symptomatic radiation pneumonitis (RP) among patients undergoing radiation therapy (RT) for non-small cell lung cancer (NSCLC). METHODS AND MATERIALS: We retrospectively identified patients who received definitive radiation therapy for stages I to III NSCLC between 2004 and 2010 at a single tertiary cancer center. Patients must have received a radiation dose of at least 60 Gy for a single primary lung tumor and have had imaging and dosimetric data available for analysis. RP was quantified according to Common Terminology Criteria for Adverse Events, version 3.0. A Cox proportional hazard model was used to assess potential associations between ACEI use and risk of symptomatic RP. RESULTS: Of 413 patients analyzed, 65 were using ACEIs during RT. In univariate analysis, the rate of RP grade  $\geq 2$  seemed lower in ACEI users than in nonusers (34% vs 46%), but this apparent difference was not statistically significant ( $P=.06$ ). In multivariate analysis of all patients, ACEI use was not associated with the risk of symptomatic RP (hazard ratio [HR] = 0.66;  $P=.07$ ) after adjustment for sex, smoking status, mean lung dose (MLD), and concurrent carboplatin and paclitaxel chemotherapy. Subgroup analysis showed that ACEI use did have a protective effect from RP grade  $\geq 2$  among patients who received a low ( $\leq 20$ -Gy) MLD ( $P<.01$ ) or were male ( $P=.04$ ). CONCLUSIONS: A trend toward reduction in symptomatic RP among patients taking ACEIs during RT for NSCLC was not statistically significant on univariate or multivariate analyses, although certain subgroups may benefit from use (ie, male patients and those receiving low MLD). The evidence at this point is insufficient to establish whether the use of ACEIs does or does not reduce the risk of RP.

[39]

**TÍTULO / TITLE:** - Histopathology predicts clinical outcome in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and debulking surgery.

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

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Dec;131(3):531-4. doi: 10.1016/j.ygyno.2013.09.030. Epub 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [1016/j.ygyno.2013.09.030](#)

**AUTORES / AUTHORS:** - Muraji M; Sudo T; Iwasaki S; Ueno S; Wakahashi S; Yamaguchi S; Fujiwara K; Nishimura R

**INSTITUCIÓN / INSTITUTION:** - Department of Gynecologic Oncology, Hyogo Cancer Center, 13-70 Kita-Oji, Akashi 6738558, Japan.

**RESUMEN / SUMMARY:** - OBJECTIVE: To analyze the factors prognostic of survival in patients with advanced epithelial ovarian cancer (EOC) treated with neoadjuvant chemotherapy (NAC) followed by interval debulking surgery. METHODS: Outcomes were retrospectively in patients with advanced EOC or peritoneal cancer who received neoadjuvant paclitaxel and carboplatin chemotherapy every 3 weeks for three to four cycles, followed by interval debulking surgery and three additional cycles of the same regimens from January 2001 to November 2010. Therapeutic response was assessed histopathologically as grade 0 to 3, based on the degree of disappearance of cancer

cells, displacement by necrotic and fibrotic tissue, and tumor-induced inflammation. Factors prognostic of progression-free survival (PFS) and overall survival (OS) were calculated. RESULTS: The 124 enrolled patients had a median age of 62years (range, 35-79years). Viable cancer cells were observed in specimens resected from 72 patients (58%) at interval debulking surgery after NAC. Multivariate analysis using the Cox proportional hazard model showed that advanced (stage IV) disease (hazard ratio [HR]=1.94, p=0.003), residual cancer at the end of surgery  $\geq 1$ cm (HR=3.78, p<0.001), and histological grade 0-1 (HR=1.65, p=0.03) were independent predictors of decreased OS. Grade 0-1 was also an independent predictor of increased risk of relapse within 6months (odds ratio=8.42, p=0.003). CONCLUSIONS: Residual disease of  $\geq 1$ cm, advanced stage, and the presence of more viable disease in resected specimens are prognostic factors for survival in advanced EOC patients receiving NAC followed by interval debulking surgery.

[40]

**TÍTULO / TITLE:** - Cladribine with Immediate Rituximab for the Treatment of Patients with Variant Hairy Cell Leukemia.

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

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

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1752](#)

**AUTORES / AUTHORS:** - Kreitman RJ; Wilson W; Calvo KR; Arons E; Roth L; Sapolsky J; Zhou H; Raffeld M; Stetler-Stevenson M

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Laboratories of Molecular Biology, Pathology, and Metabolism Branch, National Cancer Institute; and Department of Laboratory Medicine, Clinical Center, NIH, Bethesda, Maryland.

**RESUMEN / SUMMARY:** - PURPOSE: In contrast with the classic form, variant hairy cell leukemia (HCLv) responds poorly to single-agent purine analogs, expresses unmutated BRAF, has shorter overall survival, and lacks effective standard therapy. No treatment has achieved a high complete remission (CR) rate even in small series, and of 39 reported cases from six studies, overall response rate after cladribine was 44% with 8% CRs. Rituximab has been found to increase the sensitivity of malignant cells to cladribine, suggesting that combination with cladribine might improve response in HCLv. To test this hypothesis, patients with HCLv were treated with simultaneous cladribine and rituximab. EXPERIMENTAL DESIGN: Patients with HCLv with 0 to 1 prior courses of cladribine received cladribine 0.15 mg/kg for days 1 to 5, with eight weekly doses of rituximab 375 mg/m<sup>2</sup> beginning day 1. Restaging was performed, and minimal residual disease (MRD) in blood and marrow was quantified using PCR, immunohistochemistry, and flow cytometry. RESULTS: By 6 months, 9 (90%) of 10 patients achieved CR, compared with 3 (8%) of 39 reported cases treated with cladribine alone (P < 0.0001). Of the 9 CRs, 8 remain free of MRD at 12 to 48 (median 27) months of follow-up. No dose-limiting toxicities were observed when beginning cladribine and rituximab on the same day, although most patients required short-term steroids to prevent and treat rituximab infusion reactions. Cytopenias in CRs resolved in 7 to 211 (median 34) days without major infections. CONCLUSION: Although cladribine alone lacks effectiveness for early or relapsed HCLv, cladribine with

immediate rituximab achieves CRs without MRD and is feasible to administer. Clin Cancer Res; 1-9. ©2013 AACR.

[41]

**TÍTULO / TITLE:** - Chemomodulation of sequential high-dose cytarabine by fludarabine in relapsed or refractory acute myeloid leukemia: a randomized trial of the AMLCG.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Oct 22. doi: 10.1038/leu.2013.297.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.297](#)

**AUTORES / AUTHORS:** - Fiegl M; Unterhalt M; Kern W; Braess J; Spiekermann K; Staib P; Gruneisen A; Wormann B; Schondube D; Serve H; Reichle A; Hentrich M; Schiel X; Sauerland C; Heinecke A; Rieger C; Beelen D; Berdel WE; Buchner T; Hiddemann W

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine III, University Hospital of Munich, Munich, Germany.

**RESUMEN / SUMMARY:** - Chemomodulation of cytarabine by fludarabine has been attributed with a higher antileukemic efficacy, but randomized trials to address this question are rare. We therefore conducted a multicenter, randomized phase III study to evaluate the antileukemic efficacy of adding fludarabine to sequential high-dose cytarabine+idarubicin (SHAI) re-induction chemotherapy in relapsed or refractory acute myeloid leukemia (AML). Patients (n=326, of which 281 were evaluable) were randomly assigned to SHAI (cytarabine, 1 g/m<sup>2</sup> bid, days 1-2 and 8-9 (3 g/m<sup>2</sup> for patients <=60 years with refractory AML or >=2<sup>nd</sup> relapse); idarubicin 10 mg/m<sup>2</sup> daily, days 3-4 and 10-11) or F-SHAI (SHAI with fludarabine, 15 mg/m<sup>2</sup>, 4 h before cytarabine). Although complete remission (CR) rates (35% SHAI and 44% F-SHAI) and overall survival did not differ between both regimens, fludarabine prolonged time to treatment failure from 2.04 to 3.38 months (median, P<0.05). Twenty-seven percent of patients proceeded to allogeneic stem cell transplantation, with a significantly higher number of patients in CR or incomplete remission in the F-SHAI group (22 vs 10%, P<0.01). In conclusion, fludarabine has a beneficial, although moderate, impact on the antileukemic efficacy of high-dose cytarabine-based salvage therapy for relapsed and refractory AML. Leukemia advance online publication, 8 November 2013; doi:10.1038/leu.2013.297.

[42]

**TÍTULO / TITLE:** - The elevated pre-operative plasma fibrinogen level is an independent negative prognostic factor for cancer-specific, disease-free and overall survival in soft-tissue sarcoma patients.

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

**REVISTA / JOURNAL:** - J Surg Oncol. 2013 Oct 7. doi: 10.1002/jso.23458.

●● Enlace al texto completo (gratis o de pago) [1002/jso.23458](#)

**AUTORES / AUTHORS:** - Szkandera J; Pichler M; Liegl-Atzwanger B; Absenger G; Stotz M; Ploner F; Stojakovic T; Samonigg H; Eberhard K; Leithner A; Gerger A

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Graz, Austria; Research Unit Genetic Epidemiology and

Pharmacogenetics, Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Graz, Australia.

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVES: Accumulating evidence indicates an important pathophysiological role of fibrinogen on tumor cell progression and metastases in different types of cancer. The aim of the present study was to evaluate the prognostic relevance of pre-operative fibrinogen levels on clinical outcome in a large cohort of STS patients. METHODS: Two hundred ninety-four consecutive STS patients were retrospectively evaluated. Cancer-specific survival (CSS), disease-free survival (DFS), and overall survival (OS) were assessed using the Kaplan-Meier curves and Cox regression models. Finally, we supplemented the well-established Kattan nomogram by the fibrinogen level and evaluated the gain of predictive accuracy of this novel nomogram by Harrell's concordance index (c-index). RESULTS: An elevated plasma fibrinogen level was significantly associated with established prognostic factors, including age, tumor grade, size, and depth ( $P < 0.05$ ). Furthermore, in multivariate analysis, increased fibrinogen levels were significantly associated with a poor outcome for CSS (HR = 2.48; 95% CI = 1.28-4.78;  $P = 0.007$ ), DFS (HR = 2.00; 95% CI = 1.11-3.60;  $P = 0.021$ ), and OS (HR = 2.20; 95% CI = 1.39-3.47;  $P < 0.001$ ). The estimated c-index was 0.747 using the original Kattan nomogram and 0.779 when the fibrinogen levels was added. CONCLUSION: The pre-operative plasma fibrinogen level may represent a strong and independent unfavorable prognostic factor for CSS, DFS and OS in STS patients. J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

[43]

**TÍTULO / TITLE:** - A Phase I Study of EZN-3042, a Novel Survivin Messenger Ribonucleic Acid (mRNA) Antagonist, Administered in Combination With Chemotherapy in Children With Relapsed Acute Lymphoblastic Leukemia (ALL): A Report From the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium.

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

**REVISTA / JOURNAL:** - J Pediatr Hematol Oncol. 2013 Oct 31.

●● [Enlace al texto completo \(gratis o de pago\) 1097/MPH.0b013e3182a8f58f](#)

**AUTORES / AUTHORS:** - Raetz EA; Morrison D; Romanos-Sirakis E; Gaynon P; Sposto R; Bhojwani D; Bostrom BC; Brown P; Eckroth E; Cassar J; Malvar J; Buchbinder A; Carroll WL

**INSTITUCIÓN / INSTITUTION:** - \*NYU Cancer Institute and Department of Pediatrics, NYU Langone Medical Center, New York daggerStaten Island University Hospital, Staten Island, NY double daggerDivision of Hematology/Oncology section signDepartment of Preventive Medicine, Keck School of Medicine, University of Southern California parallelChildren's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA paragraph signSt. Jude Children's Research Hospital, Memphis, TN #Pediatric Hematology and Oncology, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN \*\*Johns Hopkins University, Baltimore, MD daggerdaggerEnzon Pharmaceuticals Inc., Piscataway, NJ.

**RESUMEN / SUMMARY:** - To address the therapeutic challenges in childhood relapsed ALL, a phase 1 study combining a survivin mRNA antagonist, EZN-3042, with reinduction chemotherapy was developed for pediatric patients with second or greater

bone marrow relapses of B-lymphoblastic leukemia. EZN-3042 was administered as a single agent on days -5 and -2 and then in combination with a 4-drug reinduction platform on days 8, 15, 22, and 29. Toxicity and the biological activity of EZN-3042 were assessed. Six patients were enrolled at dose level 1 (EZN-3042 2.5 mg/kg/dose). Two dose-limiting toxicities were observed: 1 patient developed a grade 3 gamma-glutamyl transferase elevation and another patient developed a grade 3 gastrointestinal bleeding. Downmodulation of survivin mRNA and protein were assessed after single-agent dosing and decreased expression was observed in 2 of 5 patients with sufficient material for analysis. Although some biological activity was observed, the combination of EZN-3042 with intensive reinduction chemotherapy was not tolerated at a dose that led to consistent downregulation of survivin expression. The trial was terminated following the completion of dose level 1, after further clinical development of this agent was halted.

[44]

**TÍTULO / TITLE:** - Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors.

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

**REVISTA / JOURNAL:** - Support Care Cancer. 2013 Oct 26.

●● Enlace al texto completo (gratis o de pago) [1007/s00520-013-2022-1](#)

**AUTORES / AUTHORS:** - Henry D; Vadhan-Raj S; Hirsh V; von Moos R; Hungria V; Costa L; Woll PJ; Scagliotti G; Smith G; Feng A; Jun S; Dansey R; Yeh H

**INSTITUCIÓN / INSTITUTION:** - Joan Karnell Cancer Center, Pennsylvania Hospital, 230 W Washington Square, Philadelphia, PA, 19106, USA, [davidhenry@pennoncology.com](mailto:davidhenry@pennoncology.com).

**RESUMEN / SUMMARY:** - PURPOSE: Bone complications of metastatic disease, including skeletal-related events (SREs), impair patients' functioning and quality of life. In a randomized, phase 3 trial of 1,776 patients with metastases from solid tumors (except breast or prostate) or multiple myeloma, denosumab was non-inferior to zoledronic acid (ZA) in delaying or preventing SREs. This ad hoc analysis reports outcomes in the subgroup of 1,597 patients with solid tumors, excluding patients with multiple myeloma. METHODS: Patients received monthly subcutaneous denosumab 120 mg or intravenous ZA 4 mg, adjusted for creatinine clearance, with calcium and vitamin D supplementation recommended. Endpoints included times to first on-study SRE, first-and-subsequent SREs, and pain worsening. RESULTS: Denosumab significantly delayed time to first on-study SRE compared with ZA (HR, 0.81; 95 % CI, 0.68-0.96) and time to first-and-subsequent SREs (RR, 0.85; 95 % CI, 0.72-1.00). Denosumab also significantly delayed time to development of moderate or severe pain (HR, 0.81; 95 % CI, 0.66-1.00), pain worsening (HR, 0.83; 95 % CI, 0.71-0.97), and worsening pain interference in patients with no/mild baseline pain (HR, 0.77; 95 % CI, 0.61-0.96). Adverse event rates were 96 % in both groups. Grade 3 or 4 hypocalcemia, mostly without clinical sequelae, was more frequent in denosumab-treated patients (denosumab 4 %, ZA 2 %). Osteonecrosis of the jaw occurred infrequently (denosumab 0.8 %, ZA 1.1 %). CONCLUSIONS: Denosumab was more effective in delaying or preventing SREs in patients with bone metastases from solid tumors and also prevented pain progression compared to ZA in this ad hoc analysis.

[45]

**TÍTULO / TITLE:** - Prostate-specific antigen changes as surrogate for overall survival in men with metastatic castration-resistant prostate cancer treated with second-line chemotherapy.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 1;31(31):3944-50. doi: 10.1200/JCO.2013.50.3201. Epub 2013 Oct 7.

•• Enlace al texto completo (gratis o de pago) [1200/JCO.2013.50.3201](#)

**AUTORES / AUTHORS:** - Halabi S; Armstrong AJ; Sartor O; de Bono J; Kaplan E; Lin CY; Solomon NC; Small EJ

**INSTITUCIÓN / INSTITUTION:** - Susan Halabi, Andrew J. Armstrong, Ellen Kaplan, Chen-Yen Lin, and Nicole C. Solomon, Duke University, Durham, NC; Oliver Sartor, Tulane University, New Orleans, LA; Johann de Bono, Royal Marsden Hospital, Sutton, United Kingdom; and Eric J. Small, University of California at San Francisco, San Francisco, CA.

**RESUMEN / SUMMARY:** - PURPOSE: Prostate-specific antigen (PSA) kinetics, and more specifically a  $\geq 30\%$  decline in PSA within 3 months after initiation of first-line chemotherapy with docetaxel, are associated with improvement in overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC). The objective of this analysis was to evaluate post-treatment PSA kinetics as surrogates for OS in patients receiving second-line chemotherapy. PATIENTS AND METHODS: Data from a phase III trial of patients with mCRPC randomly assigned to cabazitaxel plus prednisone (C + P) or mitoxantrone plus prednisone were used. PSA decline ( $\geq 30\%$  and  $\geq 50\%$ ), velocity, and rise within the first 3 months of treatment were evaluated as surrogates for OS. The Prentice criteria, proportion of treatment explained (PTE), and meta-analytic approaches were used as measures of surrogacy. RESULTS: The observed hazard ratio (HR) for death for patients treated with C + P was 0.66 (95% CI, 0.55 to 0.79;  $P < .001$ ). Furthermore, a  $\geq 30\%$  decline in PSA was a statistically significant predictor of OS (HR for death, 0.52; 95% CI, 0.43 to 0.64;  $P < .001$ ). Adjusting for treatment effect, the HR for a  $\geq 30\%$  PSA decline was 0.50 (95% CI, 0.40 to 0.62;  $P < .001$ ), but treatment remained statistically significant, thus failing the third Prentice criterion. The PTE for a  $\geq 30\%$  decline in PSA was 0.34 (95% CI, 0.11 to 0.56), indicating a lack of surrogacy for OS. The values of  $R^2$  were  $< 1$ , suggesting that PSA decline was not surrogate for OS. CONCLUSION: Surrogacy for any PSA-based end point could not be demonstrated in this analysis. Thus, the benefits of cabazitaxel in mediating a survival benefit are not fully captured by early PSA changes.

[46]

**TÍTULO / TITLE:** - Galectin-1 Is an Independent Prognostic Factor for Local Recurrence and Survival After Definitive Radiation Therapy for Patients With Squamous Cell Carcinoma of the Uterine Cervix.

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

**REVISTA / JOURNAL:** - Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):975-82. doi: 10.1016/j.ijrobp.2013.08.037. Epub 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1016/i.ijrobp.2013.08.037](http://1016/i.ijrobp.2013.08.037)

**AUTORES / AUTHORS:** - Huang EY; Chanchien CC; Lin H; Wang CC; Wang CJ; Huang CC

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

**RESUMEN / SUMMARY:** - **PURPOSE:** To investigate the role of galectin-1 in patients with cervical cancer after definitive radiation therapy. **METHODS AND MATERIALS:** We reviewed 154 patients with International Federation of Gynecology and Obstetrics stage I-II squamous cell carcinoma. Patients underwent curative-intent radiation therapy. Paraffin-embedded tissues were analyzed using immunohistochemistry staining for galectin-1. The rates of cancer-specific survival (CSS), local recurrence (LR), and distant metastasis were compared among patient tissue samples with no, weak, and strong galectin-1 expression. The Kaplan-Meier method and the Cox proportional hazard model with hazard ratios and 95% confidence intervals (CIs) were used for univariate and multivariate analyses, respectively. **RESULTS:** The areas under the curve for the intracellular expression scores of galectin-1 for both LR and CSS were significantly higher than those for stromal expression. There were no significant differences in the demographic data, such as stage and serum tumor markers, between patients with and without intracellular expression of galectin-1 in cancer tissue samples. Using multivariate analyses, the hazard ratios of LR and CSS were 2.60 (95% CI 1.50-4.52) (P=.001) and 1.94 (95% CI 1.18-3.19) (P=.010), respectively. **CONCLUSION:** Galectin-1 is an independent prognostic factor associated with LR and CSS in stage I-II cervical cancer patients undergoing definitive radiation therapy. Further studies targeting galectin-1 may improve the local control of cervical cancer.

[47]

**TÍTULO / TITLE:** - Level of HER2 Gene Amplification Predicts Response and Overall Survival in HER2-Positive Advanced Gastric Cancer Treated With Trastuzumab.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2013.48.9070](http://1200/JCO.2013.48.9070)

**AUTORES / AUTHORS:** - Gomez-Martin C; Plaza JC; Pazo-Cid R; Salud A; Pons F; Fonseca P; Leon A; Alsina M; Visa L; Rivera F; Galan MC; Del Valle E; Vilardell F; Iglesias M; Fernandez S; Landolfi S; Cuatrecasas M; Mayorga M; Jose Paules M; Sanz-Moncasi P; Montagut C; Garralda E; Rojo F; Hidalgo M; Lopez-Rios F

**INSTITUCIÓN / INSTITUTION:** - Carlos Gomez-Martin, Elena Garralda, and Manuel Hidalgo, Spanish National Cancer Research Centre; Carlos Gomez-Martin, Jose Carlos Plaza, Fernando Lopez-Rios, and Manuel Hidalgo, Laboratorio Dianas Terapeuticas, Centro Integral Oncologico Clara Campal, Hospital Universitario Sanchinarro; Federico Rojo and Ana Leon, Fundacion Jimenez Diaz, Madrid; Pilar Sanz-Moncasi, Hospital Royo-Villanova; Roberto Pazo-Cid and Elena del Valle, Hospital Universitario Miguel Servet, Zaragoza; Antonieta Salud and Felipe Vilardell, Hospital Universitario Arnau de Vilanova, Lerida; Francesc Pons, Mar Iglesias, and Clara Montagut, Hospital de Mar; Maria Alsina and Stefania Landolfi, Hospital

Universitari Vall d'Hebron; M. Carmen Galan and M. Jose Paules, Instituto Catalan de Oncologia; Miriam Cuatrecasas and Laura Visa, Hospital Clinic Universitari, Barcelona; Paula Fonseca and Soledad Fernandez, Hospital Universitario Central de Asturias, Oviedo; Fernando Rivera and Marta Mayorga, Hospital Universitario Marques de Valdecilla, Santander, España.

**RESUMEN / SUMMARY:** - PURPOSE: Previous studies have highlighted the importance of an appropriate human epidermal growth factor receptor 2 (HER2) evaluation for the proper identification of patients eligible for treatment with anti-HER2 targeted therapies. Today, the relationship remains unclear between the level of HER2 amplification and the outcome of HER2-positive gastric cancer treated with first-line chemotherapy with trastuzumab. The aim of this study was to determine whether the level of HER2 gene amplification determined by the HER2/CEP17 ratio and HER2 gene copy number could significantly predict some benefit in overall survival and response to therapy in advanced gastric cancer treated with trastuzumab-based chemotherapy. PATIENTS AND METHODS: Ninety patients with metastatic gastric cancer treated with first-line trastuzumab-based chemotherapy were studied. The optimal cutoff values for HER2/CEP17 ratio and HER2 gene copy number (GCN) for discriminating positive results in terms of response and prolonged survival were determined using receiver operating characteristic curves analyses. RESULTS: In this study, a median HER2/CEP17 ratio of 6.11 (95% CI, 2.27 to 21.90) and a median HER2 gene copy number of 11.90 (95% CI, 3.30 to 43.80) were found. A mean HER2/CEP17 ratio of 4.7 was identified as the optimal cutoff value discriminating sensitive and refractory patients (P = .005). Similarly, the optimal cutoff for predicting survival longer than 12 months was 4.45 (P = .005), and for survival longer than 16 months was 5.15 (P = .004). For HER2 GCN, the optimal cutoff values were 9.4, 10.0, and 9.5, respectively (P = .02). CONCLUSION: The level of HER2 gene amplification significantly predicts sensitivity to therapy and overall survival in advanced gastric cancer treated with trastuzumab-based chemotherapy.

[48]

**TÍTULO / TITLE:** - CXCR3/CCR5 pathways in metastatic melanoma patients treated with adoptive therapy and interleukin-2.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 29;109(9):2412-23. doi: 10.1038/bjc.2013.557. Epub 2013 Oct 15.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.557](#)

**AUTORES / AUTHORS:** - Bedognetti D; Spivey TL; Zhao Y; Uccellini L; Tomei S; Dudley ME; Ascierto ML; De Giorgi V; Liu Q; Delogu LG; Sommariva M; Sertoli MR; Simon R; Wang E; Rosenberg SA; Marincola FM

**INSTITUCIÓN / INSTITUTION:** - 1] Infectious Disease and Immunogenetics Section (IDIS), Department of Transfusion Medicine, Clinical Center and trans-NIH Center for Human Immunology (CHI), National Institutes of Health, Bethesda, MD 20892, USA [2] Department of Oncology, Biology, Genetics (DOBIG), University of Genoa and National Cancer Research Institute, 16132 Genoa, Italy [3] Department of Internal Medicine (DiMI), University of Genoa, 16132 Genoa, Italy.

**RESUMEN / SUMMARY:** - Background: Adoptive therapy with tumour-infiltrating lymphocytes (TILs) induces durable complete responses (CR) in approximately 20% of

patients with metastatic melanoma. The recruitment of T cells through CXCR3/CCR5 chemokine ligands is critical for immune-mediated rejection. We postulated that polymorphisms and/or expression of CXCR3/CCR5 in TILs and the expression of their ligands in tumour influence the migration of TILs to tumours and tumour regression. Methods: Tumour-infiltrating lymphocytes from 142 metastatic melanoma patients enrolled in adoptive therapy trials were genotyped for CXCR3 rs2280964 and CCR5-Delta32 deletion, which encodes a protein not expressed on the cell surface. Expression of CXCR3/CCR5 in TILs and CXCR3/CCR5 and ligand genes in 113 available parental tumours was also assessed. Tumour-infiltrating lymphocyte data were validated by flow cytometry (N=50). Results: The full gene expression/polymorphism model, which includes CXCR3 and CCR5 expression data, CCR5-Delta32 polymorphism data and their interaction, was significantly associated with both CR and overall response (OR; P=0.0009, and P=0.007, respectively). More in detail, the predicted underexpression of both CXCR3 and CCR5 according to gene expression and polymorphism data (protein prediction model, PPM) was associated with response to therapy (odds ratio=6.16 and 2.32, for CR and OR, respectively). Flow cytometric analysis confirmed the PPM. Coordinate upregulation of CXCL9, CXCL10, CXCL11, and CCL5 in pretreatment tumour biopsies was associated with OR. Conclusion: Coordinate overexpression of CXCL9, CXCL10, CXCL11, and CCL5 in pretreatment tumours was associated with responsiveness to treatment. Conversely, CCR5-Delta32 polymorphism and CXCR3/CCR5 underexpression influence downregulation of the corresponding receptors in TILs and were associated with likelihood and degree of response.

[49]

**TÍTULO / TITLE:** - Early PET/CT Scan Is More Effective Than RECIST in Predicting Outcome of Patients with Liver Metastases from Colorectal Cancer Treated with Preoperative Chemotherapy Plus Bevacizumab.

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

**REVISTA / JOURNAL:** - J Nucl Med. 2013 Dec;54(12):2062-9. doi: 10.2967/jnumed.113.119909. Epub 2013 Oct 17.

●● [Enlace al texto completo \(gratis o de pago\) 2967/jnumed.113.119909](#)

**AUTORES / AUTHORS:** - Latoria S; Piccirillo MC; Caraco C; Nasti G; Aloj L; Arrichiello C; de Lutio di Castelguidone E; Tatangelo F; Ottaiano A; Iaffaioli RV; Izzo F; Romano G; Giordano P; Signoriello S; Gallo C; Perrone F

**INSTITUCIÓN / INSTITUTION:** - Nuclear Medicine Unit, Istituto Nazionale Tumori "Fondazione G. Pascale" - IRCCS, Naples, Italy.

**RESUMEN / SUMMARY:** - Markers predictive of treatment effect might be useful to improve the treatment of patients with metastatic solid tumors. Particularly, early changes in tumor metabolism measured by PET/CT with (18)F-FDG could predict the efficacy of treatment better than standard dimensional Response Evaluation Criteria In Solid Tumors (RECIST) response. METHODS: We performed PET/CT evaluation before and after 1 cycle of treatment in patients with resectable liver metastases from colorectal cancer, within a phase 2 trial of preoperative FOLFIRI plus bevacizumab. For each lesion, the maximum standardized uptake value (SUV) and the total lesion glycolysis (TLG) were determined. On the basis of previous studies, a  $\leq -50\%$  change from baseline was used as a threshold for significant metabolic response for

maximum SUV and, exploratively, for TLG. Standard RECIST response was assessed with CT after 3 mo of treatment. Pathologic response was assessed in patients undergoing resection. The association between metabolic and CT/RECIST and pathologic response was tested with the McNemar test; the ability to predict progression-free survival (PFS) and overall survival (OS) was tested with the Log-rank test and a multivariable Cox model. RESULTS: Thirty-three patients were analyzed. After treatment, there was a notable decrease of all the parameters measured by PET/CT. Early metabolic PET/CT response (either SUV- or TLG-based) had a stronger, independent and statistically significant predictive value for PFS and OS than both CT/RECIST and pathologic response at multivariate analysis, although with different degrees of statistical significance. The predictive value of CT/RECIST response was not significant at multivariate analysis. CONCLUSION: PET/CT response was significantly predictive of long-term outcomes during preoperative treatment of patients with liver metastases from colorectal cancer, and its predictive ability was higher than that of CT/RECIST response after 3 mo of treatment. Such findings need to be confirmed by larger prospective trials.

[50]

**TÍTULO / TITLE:** - Azadirone, a Limonoid Tetranortriterpene, Induces Death Receptors and Sensitizes Human Cancer Cells to Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL) through a p53 Protein-independent Mechanism: EVIDENCE FOR THE ROLE OF THE ROS-ERK-CHOP-DEATH RECEPTOR PATHWAY.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 8;288(45):32343-56. doi: 10.1074/jbc.M113.455188. Epub 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.455188](#)

**AUTORES / AUTHORS:** - Gupta SC; Francis SK; Nair MS; Mo YY; Aggarwal BB

**INSTITUCIÓN / INSTITUTION:** - From the Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030.

**RESUMEN / SUMMARY:** - Although tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has shown efficacy in a phase 2 clinical trial, development of resistance to TRAIL by tumor cells is a major roadblock. We investigated whether azadirone, a limonoidal tetranortriterpene, can sensitize human tumor cells to TRAIL. Results indicate that azadirone sensitized cancer cells to TRAIL. The limonoid induced expression of death receptor (DR) 5 and DR4 but did not affect expression of decoy receptors in cancer cells. The induction of DRs was mediated through activation of ERK and through up-regulation of a transcription factor CCAAT enhancer-binding protein homologous protein (CHOP) as silencing of these signaling molecules abrogated the effect of azadirone. These effects of azadirone were cancer cell-specific. The CHOP binding site on the DR5 gene was required for induction of DR5 by azadirone. Up-regulation of DRs was mediated through the generation of reactive oxygen species (ROS) as ROS scavengers reduced the effect of azadirone on ERK activation, CHOP up-regulation, DR induction, and TRAIL sensitization. The induction of DRs by this limonoid was independent of p53, but sensitization to TRAIL was p53-dependent. The limonoid down-regulated the expression of cell survival proteins and up-regulated the proapoptotic proteins. The combination of azadirone with TRAIL was

found to be additive at concentrations lower than IC50, whereas at higher concentrations, the combination was synergistic. Overall, this study indicates that azadirone can sensitize cancer cells to TRAIL through ROS-ERK-CHOP-mediated up-regulation of DR5 and DR4 signaling, down-regulation of cell survival proteins, and up-regulation of proapoptotic proteins.

[51]

**TÍTULO / TITLE:** - miR-181a is associated with poor clinical outcome in patients with colorectal cancer treated with EGFR inhibitor.

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

**REVISTA / JOURNAL:** - J Clin Pathol. 2013 Oct 4. doi: 10.1136/jclinpath-2013-201904.

●● Enlace al texto completo (gratis o de pago) [1136/jclinpath-2013-201904](#)

**AUTORES / AUTHORS:** - Pichler M; Winter E; Rössl AL; Bauernhofer T; Gerger A; Kiesslich T; Lax S; Samonigg H; Hoefler G

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology, Department of Internal Medicine, Medical University of Graz (MUG), Graz, Austria.

**RESUMEN / SUMMARY:** - AIMS: miR-181a expression is frequently altered in different types of cancer. Members of the Wnt/beta-catenin signalling pathway, which is commonly altered in colorectal cancer (CRC), have been reported as molecular interaction partners of miR-181. However, the role of miR-181a expression in CRC and its ability to predict survival and response to agents targeting the epidermal growth factor receptor (EGFR) have not been explored yet. METHODS: In this study, we analysed 80 patients with wild type KRAS CRC undergoing treatment with the EGFR-targeting monoclonal antibodies cetuximab and panitumumab for metastatic CRC. The KRAS mutational status was determined by pyrosequencing and miR-181a expression was measured by quantitative RT-PCR in CRC tumour tissue and corresponding non-neoplastic colon tissue. The microRNA expression levels were correlated with clinicopathological characteristics. Cancer-specific survival was calculated by univariate and multivariate analyses, and progression-free survival (PFS) during treatment with EGFR-targeting agents was also evaluated. RESULTS: A low miR-181a expression level was associated with poor differentiation of CRC (p=0.04). A Kaplan-Meier curve showed a decreased survival time for patients with low miR-181a expression (p=0.019). Low miR-181a expression was furthermore associated with poor PFS (p=0.015). CONCLUSIONS: In conclusion, our data suggest that the miR-181a expression level is associated with poor survival in patients with CRC. Furthermore, miR-181a expression might predict PFS in EGFR-targeted therapy.

[52]

**TÍTULO / TITLE:** - Autoimmune Disease, Tumor Necrosis Factor Inhibitors and Acute Leukemia: Possible Associations in Two Patients?

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Nov 4.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.861069](#)

**AUTORES / AUTHORS:** - Ozen M; Keskin O; Topcuoglu P; Ozturk B; Ozgul S; Ilgen U; Kucuksahin O; Turgay M; Toruner M; Gurman G

[53]

**TÍTULO / TITLE:** - CK-19 mRNA-positive cells in peripheral blood predict treatment efficacy and survival in small-cell lung cancer patients.

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

**REVISTA / JOURNAL:** - Med Oncol. 2013 Dec;30(4):755. doi: 10.1007/s12032-013-0755-9. Epub 2013 Nov 1.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0755-9](#)

**AUTORES / AUTHORS:** - Shi WL; Li J; Du YJ; Zhu WF; Wu Y; Hu YM; Chen YC

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary Medicine, Affiliated Hospital of Jiangsu University, 438 North Jiefang Street, Zhenjiang, 212001, China.

**RESUMEN / SUMMARY:** - Small-cell lung cancer (SCLC) is the most aggressive form of lung cancer. The aim of this study was to investigate whether the presence of cytokeratin-19 (CK-19) mRNA-positive circulating tumor cells (CTCs) predicts treatment response, progression-free survival (PFS), and overall survival (OS) in SCLC patients who received standard therapy. Fifty-five SCLC patients were enrolled in this single-center prospective study. CK-19 mRNA-positive CTCs in blood samples were detected using real-time quantitative-PCR assay before the initiation of chemotherapy (B0) and after one chemotherapy cycle (B1) and three chemotherapy cycles (B3). The association with known prognostic factors and the effect of CK-19 mRNA-positive CTCs on patients' prognosis were analyzed. Patients with positivity for CK-19 mRNA-positive CTCs at B0, B1, and B3 time points had shorter PFS and OS compared with patients without ( $P = 0.014$  and  $P = 0.01$ , respectively, at B0;  $P = 0.008$  and  $P = 0.002$ , respectively, at B1;  $P = 0.003$  and  $P = 0.001$ , respectively, at B3). Conversion of initial positivity for CK-19 mRNA-positive CTCs to negativity at B1 and B3 time points was associated with longer PFS and OS compared with patients with persistent positivity at three time points ( $P = 0.008$  and  $P = 0.010$ , respectively). Multivariate analysis demonstrated that the presence of CK-19 mRNA-positive CTCs at B0, B1, and B3 time points remained strong predictors of PFS and OS after adjustment for clinically significant factors. In conclusion, detection of CK-19 mRNA-positive CTCs before and during chemotherapy is an accurate indication of subsequent disease progression and mortality for SCLC patients.

[54]

**TÍTULO / TITLE:** - Rebiopsy of non-small cell lung cancer patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor: Comparison between T790M mutation-positive and mutation-negative populations.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Sep 16. doi: 10.1002/cncr.28364.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28364](#)

**AUTORES / AUTHORS:** - Hata A; Katakami N; Yoshioka H; Takeshita J; Tanaka K; Nanjo S; Fujita S; Kaji R; Imai Y; Monden K; Matsumoto T; Nagata K; Otsuka K; Tachikawa R; Tomii K; Kunimasa K; Iwasaku M; Nishiyama A; Ishida T; Nishimura Y

**INSTITUCIÓN / INSTITUTION:** - Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: The secondary epidermal growth factor receptor (EGFR) mutation Thr790Met (T790M) accounts for approximately half of

acquired resistances to EGFR-tyrosine kinase inhibitor (TKI). Recent reports have demonstrated that the emergence of T790M predicts a favorable prognosis and indolent progression. However, rebiopsy to confirm T790M status can be challenging due to limited tissue availability and procedural feasibility, and little is known regarding the differences among patients with or without T790M mutation. METHODS: The study investigated 78 EGFR-mutant patients who had undergone rebiopsy after TKI failure. The peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method was used in EGFR mutational analyses. Various patient characteristics and postprogression survivals (PPSs) after initial TKI failure were retrospectively compared in patients with and without T790M. RESULTS: The T790M mutation was identified in 4 (17%) of 24 central nervous system lesions, and in 22 (41%) of 54 other lesions ( $P = .0417$ ). No other characteristics had a statistical association with T790M prevalence. Median PPS was 31.4 months in 26 patients with T790M, and 11.4 months in 52 patients without T790M ( $P = .0017$ ). In the multivariate analysis, statistically significant factors for longer PPS included T790M-positive, good performance status, and no carcinomatous meningitis. CONCLUSIONS: The emergence of T790M in central nervous system lesions was rare, compared with other lesions. Patients with T790M after TKI failure appear to have better prognoses than those without T790M. TKI rechallenge or continuous administration beyond progression may be effective after initial TKI failure. Cancer 2013. © 2013 American Cancer Society.

[55]

**TÍTULO / TITLE:** - Intensive induction is effective in select octogenarian acute myeloid leukemia patients: prognostic significance of karyotype and selected molecular markers used in the European LeukemiaNet classification.

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

**REVISTA / JOURNAL:** - Haematologica. 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.092072](#)

**AUTORES / AUTHORS:** - Wetzler M; Mrozek K; Kohlschmidt J; Dombret H; Dohner H; Pilorge S; Krug U; Carroll AJ; Larson RA; Marcucci G; Hiddemann W; Buchner T; Bloomfield C

**INSTITUCIÓN / INSTITUTION:** - USA;

**RESUMEN / SUMMARY:** - We investigated whether octogenarian patients with acute myeloid leukemia enrolled onto Cooperative Group clinical trials and treated with intensive induction therapy could be cured, and whether karyotype and selected molecular markers had any prognostic significance in these patients. Among 138 patients with cytogenetic results, normal karyotype was the most common (47.1%) followed by complex karyotype (14.5%) and sole +8 (9.4%). Among these patients, the relapse-free survival (RFS) rate at 1 year was 37% and 13% at 3 years, and the respective overall survival (OS) rates were 24% and 8%. Whereas the 90 patients who survived beyond 30 days had the same RFS rates, their 1-year and 3-year OS rates were 36% and 11%, respectively. Of the 66 patients surviving beyond 30 days who could be classified into the European LeukemiaNet (ELN) Genetic Groups, those in the Intermediate-I Group had better OS than patients in the Adverse Group ( $P=.01$ ). Among patients with cytogenetically normal acute myeloid leukemia who were tested for the ELN-associated molecular alterations, FLT3-internal tandem duplication and NPM1 mutations, FLT3-internal tandem duplication (detected in 29% of patients) did

not associate with OS ( $P=.31$ ), whereas NPM1 mutations (30%) were associated with a significantly longer OS ( $P=.002$ ). We conclude that intensive induction is effective and indicated in selected octogenarians with acute myeloid leukemia, that their OS varies among the ELN Genetic Groups and that NPM1 mutations may be of prognostic significance among octogenarian patients with cytogenetically normal acute myeloid leukemia.

[56]

**TÍTULO / TITLE:** - The apoptotic and proliferation rate of tumour budding cells in colorectal cancer outlines a heterogeneous population of cells with various impacts on clinical outcome.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Oct 1. doi: 10.1111/his.12294.

●● [Enlace al texto completo \(gratis o de pago\) 1111/his.12294](#)

**AUTORES / AUTHORS:** - Dawson H; Koelzer VH; Karamitopoulou E; Economou M; Hammer C; Muller DE; Lugli A; Zlobec I

**INSTITUCIÓN / INSTITUTION:** - Clinical Pathology Division, University of Bern, Switzerland.

**RESUMEN / SUMMARY:** - In colorectal cancer (CRC), tumour buds represent an aggressive cell type at the invasive front with apparently low proliferation. AIMS: To determine proliferation and apoptotic rates of buds in comparison to tumour centre, front and mucosa. METHODS AND RESULTS: Whole tissue sections from 188 CRC patients underwent immunohistochemistry for Ki67. 10 high-power-fields (HPFs) were evaluated in mucosa, tumour centre, front and buds (total=40 HPFs/case). Caspase-3 and M30Cytodeath immunohistochemistry was performed on a multi-punch tissue microarray from the same cohort. Ki67, Caspase-3 and M30Cytodeath immunoreactivity was correlated to outcome. Average Ki67 positivity was 5.2% in mucosa without significant difference between centre and front (38.2% and 34.9%;  $p<0.0001$ ). 0.3% of buds showed Ki67 positivity ( $p<0.0001$ ). Caspase-3 was similar in mucosa, tumour centre and front while lower in buds ( $<0.1\%$ ;  $p<0.0001$ ). M30Cytodeath staining in buds was decreased (0.01%;  $p<0.0001$ ) in comparison to other areas. Ki67 positivity in buds was detrimental to survival in univariate ( $p=0.0352$ ) and multivariate ( $p=0.0355$ ) analysis. Caspase-3 positive tumours showed better outcome ( $p=0.0262$ ), this was inverse in buds ( $p=0.0235$ ). CONCLUSIONS: Ki67, Caspase-3 and M30Cytodeath staining is absent in most buds, suggesting decreased proliferation and apoptosis. However, Ki67 and Caspase-3 immunoreactivity associated with unfavourable prognosis points to a heterogeneous population of tumour buds. This article is protected by copyright. All rights reserved.

[57]

**TÍTULO / TITLE:** - Clinical Outcomes After First-line EGFR Inhibitor Treatment for Patients with NSCLC, EGFR Mutation, and Poor Performance Status.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):5057-64.

**AUTORES / AUTHORS:** - Okuma Y; Hosomi Y; Nagamata M; Yamada Y; Sekihara K; Kato K; Hishima T; Okamura T

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo, Tokyo 113-8677, Japan. [y-okuma@cick.jp](mailto:y-okuma@cick.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The phase II NEJ001 trial suggested that gefitinib was active against advanced non-small cell lung cancer (NSCLC) even in patients with poor performance status (PS). Clinical response among the patients harboring epidermal growth factor receptor (EGFR) mutation with poor PS is fair; however, gefitinib does not have as much continued efficacy as in patients with good PS. This study has retrospectively investigated the clinical outcomes of gefitinib treated patients with advanced NSCLC, EGFR mutations, and poor PS. PATIENTS AND METHODS: A total of 208 patients with advanced NSCLC and poor PS treated with gefitinib from 2004 to 2013 were retrospectively evaluated. Outcomes were studied after stratification for gender, smoking status, histological subtype, and EGFR mutation status. RESULTS: Fifty-two patients (25.0%) with advanced NSCLC, EGFR mutation, and poor PS were treated with gefitinib. The overall response rate was 65.4%. The median progression-free survival, median survival time, and one-year survival rate was 6.6 months, 19.6 months, and 62.9%, respectively. Death due to interstitial lung disease occurred in 11.5% of the patient population. In multivariate analysis, a PS of 4 was independently associated with poor outcomes (hazard ratio=10.5; 95% Confidence interval=1.92-50.19; p=0.0091). CONCLUSION: Patients with advanced NSCLC, EGFR mutation, and poor PS have poor outcomes in response to gefitinib. However, the indication of gefitinib for such patients will not be changed in clinical practice and oncologists should treat these patients with more careful follow-up since for those with poor PS, therapy may be more toxic than for patients with good PS.

[58]

**TÍTULO / TITLE:** - Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 7. doi: 10.1038/bjc.2013.701.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.701](https://doi.org/10.1038/bjc.2013.701)

**AUTORES / AUTHORS:** - Szkandera J; Stotz M; Absenger G; Stojakovic T; Samonigg H; Kornprat P; Schaberl-Moser R; Alzoughbi W; Lackner C; Ressa AL; Seggewies FS; Gerger A; Hoefler G; Pichler M

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria.

**RESUMEN / SUMMARY:** - Background:Recent evidence indicates that the host inflammatory response has an important role in the tumour progression. Elevated C-reactive protein (CRP) levels have been previously associated with poor prognosis in several cancer types including small-scale studies in pancreatic cancer (PC) patients. The purpose of the present study was to validate the prognostic impact of plasma CRP levels at date of diagnosis on cancer-specific survival (CSS) in a large cohort of PC patients.Methods:Data from 474 consecutive patients with adenocarcinoma of the pancreas, treated between 2004 and 2012 at a single centre, were evaluated retrospectively. CSS was analysed using the Kaplan-Meier method. To evaluate the prognostic significance of plasma CRP levels, univariate and multivariate Cox analyses

were applied. Results: High plasma CRP levels at diagnosis were significantly associated with well-established prognostic factors, including high tumour stage and tumour grade and the administration of chemotherapy ( $P < 0.05$ ). In univariate analysis, we observed that a high plasma CRP level was a consistent factor for poor CSS in PC patients (hazard ratio (HR)=2.21; 95% confidence interval (CI)=1.68-2.92,  $P < 0.001$ ). In multivariate analysis, tumour stage, grade, administration of chemotherapy, a high neutrophil-lymphocyte ratio and the highest quartile of CRP levels (HR=1.60, 95% CI=1.16-2.21;  $P = 0.005$ ) were identified as independent prognostic factors in PC patients. Conclusion: In conclusion, we confirmed a significant association of elevated CRP levels with poor clinical outcome in PC patients. Our results indicate that the plasma CRP level might represent a useful marker for patient stratification in PC management. British Journal of Cancer advance online publication, 7 November 2013; doi:10.1038/bjc.2013.701 [www.bjcancer.com](http://www.bjcancer.com).

[59]

**TÍTULO / TITLE:** - Correlation of Smad4 status with outcomes in patients receiving erlotinib combined with adjuvant chemoradiation and chemotherapy after resection for pancreatic adenocarcinoma.

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

**REVISTA / JOURNAL:** - Int J Radiat Oncol Biol Phys. 2013 Nov 1;87(3):458-9. doi: 10.1016/j.ijrobp.2013.06.2039.

●● Enlace al texto completo (gratis o de pago) [1016/j.ijrobp.2013.06.2039](http://1016/j.ijrobp.2013.06.2039)

**AUTORES / AUTHORS:** - Herman JM; Fan KY; Wild AT; Wood LD; Blackford AL; Donehower RC; Hidalgo M; Schulick RD; Edil BH; Choti MA; Hruban RH; Pawlik TM; Cameron JL; Laheru DA; Iacobuzio-Donahue CA; Wolfgang CL

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology & Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland. Electronic address:

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[60]

**TÍTULO / TITLE:** - Safety, Pharmacokinetics, Pharmacodynamics and Antitumor Activity of Dalantercept, an Activin Receptor-Like Kinase-1 Ligand Trap, in Patients with Advanced Cancer.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Oct 30.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-](http://1158/1078-0432.CCR-13-1840)

[1840](#)

**AUTORES / AUTHORS:** - Bendell JC; Gordon MS; Hurwitz HI; Jones SF; Mendelson DS; Blobe GC; Agarwal N; Condon CH; Wilson D; Pearsall AE; Yang Y; McClure T; Attie KM; Sherman ML; Sharma S

**INSTITUCIÓN / INSTITUTION:** - Gastrointestinal Research, Sarah Cannon Research Institute.

**RESUMEN / SUMMARY:** - PURPOSE: The angiogenesis inhibitor dalantercept (formerly ACE-041) is a soluble form of activin receptor-like kinase-1 (ALK1) that prevents activation of endogenous ALK1 by bone morphogenetic protein-9 (BMP9) and BMP10,

and exhibits antitumor activity in preclinical models. This first-in-human study of dalantercept evaluated its safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity in adults with advanced solid tumors. EXPERIMENTAL DESIGN: Patients in dose-escalating cohorts received dalantercept subcutaneously at one of seven dose levels (0.1 to 4.8 mg/kg) every 3 weeks until disease progression. Patients in an expansion cohort received dalantercept at 0.8 or 1.6 mg/kg every 3 weeks until disease progression. RESULTS: In 37 patients receiving dalantercept, the most common treatment-related adverse events were peripheral edema, fatigue and anemia. Edema and fluid retention were dose-limiting toxicities, and responded to diuretic therapy. No clinically significant, treatment-related hypertension, proteinuria, gross hemorrhage or gastrointestinal perforations were observed. One patient with refractory squamous cell cancer of the head and neck had a partial response, and 13 patients had stable disease according to RECISTv1.1, eight of whom had prolonged periods ( $\geq 12$  weeks) of stable disease. Correlative pharmacodynamic markers included tumor metabolic activity and tumor blood flow, which decreased from baseline in 63% and 82% of evaluable patients, respectively, and telangiectasia in eight patients. CONCLUSION: Dalantercept was well tolerated at doses up to 1.6 mg/kg, with a safety profile distinct from inhibitors of the vascular endothelial growth factor pathway. Dalantercept displayed promising antitumor activity in patients with advanced refractory cancer, and multiple phase II studies are underway.

[61]

**TÍTULO / TITLE:** - Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: Analysis of the Greek myeloma study group.

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

**REVISTA / JOURNAL:** - Am J Hematol. 2013 Oct 3. doi: 10.1002/ajh.23600.

●● Enlace al texto completo (gratis o de pago) [1002/ajh.23600](#)

**AUTORES / AUTHORS:** - Katodritou E; Terpos E; Kelaidi C; Kotsopoulou M; Delimpasi S; Kyrtsionis MC; Symeonidis A; Giannakoulas N; Stefanoudaki A; Christoulas D; Chatziaggelidou C; Gastari V; Spyridis N; Verrou E; Konstantinidou P; Zervas K; Dimopoulos MA

**INSTITUCIÓN / INSTITUTION:** - Hematology Department, Theagenion Cancer Hospital, Thessaloniki, Greece.

**RESUMEN / SUMMARY:** - Plasma cell leukemia (PCL) is a rare and aggressive plasma cell disorder, with poor outcome. Bortezomib-based regimens (BBR) are highly effective in myeloma, but there is limited information about their efficacy and safety in PCL. Thus, we retrospectively collected data from 42 consecutive PCL patients (25 with primary PCL-pPCL and 17 with secondary PCL-sPCL) to explore the role of BBR in this entity. BBR were administered in 29 of 42 patients, while 6 of 25 patients with pPCL underwent autologous transplantation. Objective response ( $\geq$ partial response) was significantly higher in patients treated with BBR versus conventional therapies (69% vs. 30.8%,  $P = 0.04$ ); 27.5% of patients treated with BBR achieved at least very good partial response (vgPR). The highest ORR was observed in pPCL patients treated with BBR (88.9%;  $\geq$ vgPR: 33.3%). In BBR-group, grade 3 of 4 hematological, neurological and renal toxicity and neutropenic infections were observed in 41.4%, 7%, 3.4%, and 31%, respectively. With a median follow-up of 51 months, median overall

survival (OS) for patients treated with BBR versus conventional therapies was 13 versus 2 months ( $P < 0.007$ ). Median OS of patients with pPCL and sPCL treated with BBR was 18 and 7 months, respectively ( $P < 0.001$ ). In the multivariate analysis normal PLTs, treatment with BBR and high quality response were the only powerful predictors for survival. Our study carrying the longest reported median follow-up, demonstrated that treatment of PCL with BBR induces high response rates and prolongs survival over conventional therapies, regardless of additional autologous transplantation rescue or established high risk features, with manageable toxicity. Am. J. Hematol., 2013. © 2013 Wiley Periodicals, Inc.

[62]

**TÍTULO / TITLE:** - The effect of metformin on apoptosis in a breast cancer presurgical trial.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2792-7. doi: 10.1038/bjc.2013.657. Epub 2013 Oct 24.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.657](#)

**AUTORES / AUTHORS:** - Cazzaniga M; Decensi A; Pruneri G; Puntoni M; Bottiglieri L; Varricchio C; Guerrieri-Gonzaga A; Gentilini OD; Pagani G; Dell'orto P; Lazzeroni M; Serrano D; Viale G; Bonanni B

**INSTITUCIÓN / INSTITUTION:** - Division of Cancer Prevention and Genetics, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy.

**RESUMEN / SUMMARY:** - Background:Metformin has been associated with antitumour activity in breast cancer (BC) but its mechanism remains unclear. We determined whether metformin induced a modulation of apoptosis by terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) overall and by insulin resistance status in a presurgical trial.Methods:Apoptosis was analysed in core biopsies and in surgical samples from 100 non-diabetic BC patients participating in a randomised trial of metformin vs placebo given for 4 weeks before surgery.Results:Eighty-seven subjects (45 on metformin and 42 on placebo) were assessable for TUNEL measurement at both time points. TUNEL levels at surgery were higher than that at baseline core biopsy ( $P < 0.0001$ ), although no difference between arms was noted (metformin arm: median difference surgery-biopsy levels +4%, interquartile range (IQR): 2-12; placebo arm: +2%, IQR: 0-8,  $P = 0.2$ ). Ki67 labelling index and TUNEL levels were directly correlated both at baseline and surgery (Spearman's  $r = 0.51$ ,  $P < 0.0001$ ). In the 59 women without insulin resistance ( $HOMA \text{ index} < 2.8$ ), there was a higher level of TUNEL at surgery on metformin vs placebo (median difference on metformin +4%, IQR: 2-14 vs +2%, IQR: 0-7 on placebo), whereas an opposite trend was found in the 28 women with insulin resistance (median difference on metformin +2%, IQR: 0-6, vs +5%, IQR: 0-15 on placebo,  $P\text{-interaction} = 0.1$ ).Conclusion:Overall, we found no significant modulation of apoptosis by metformin, although there was a trend to a different effect according to insulin resistance status, with a pattern resembling Ki67 changes. Apoptosis was significantly higher in the surgical specimens compared with baseline biopsy and was directly correlated with Ki67. Our findings provide additional evidence for a dual effect of metformin on BC growth according to insulin resistance status.

[63]

**TÍTULO / TITLE:** - Expression of TP53 mutation-associated microRNAs predicts clinical outcome in head and neck squamous cell carcinoma patients.

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

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Dec;24(12):3082-8. doi: 10.1093/annonc/mdt380. Epub 2013 Oct 9.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt380](#)

**AUTORES / AUTHORS:** - Ganci F; Sacconi A; Bossel Ben-Moshe N; Manciocco V; Sperduti I; Strigari L; Covello R; Benevolo M; Pescarmona E; Domany E; Muti P; Strano S; Spriano G; Fontemaggi G; Blandino G

**INSTITUCIÓN / INSTITUTION:** - Translational Oncogenomics Unit, Italian National Cancer Institute 'Regina Elena', Rome, Italy.

**RESUMEN / SUMMARY:** - BACKGROUND: TP53 mutation is associated with decreased survival rate in head and neck squamous cell carcinoma (HNSCC) patients. We set out to identify microRNAs (miRNAs) whose expression associates with TP53 mutation and survival in HNSCC. PATIENTS AND METHODS: We analyzed TP53 status by direct sequencing of exons 2 through 11 of a prospective series of 121 HNSCC samples and assessed its association with outcome in 109 followed-up patients. We carried out miRNA expression profiling on 121 HNSCC samples and 66 normal counterparts. miRNA associations with TP53 mutations and outcome were evaluated. RESULTS: A TP53 mutation was present in 58% of the tumors and TP53 mutations were significantly associated with a shorter recurrence-free survival. This association was stronger in the clinical subgroup of patients subjected to adjuvant therapy after surgery. The expression of 49 miRNAs was significantly associated with TP53 status. Among these 49, we identified a group of 12 miRNAs whose expression correlates with recurrence-free survival and a group of 4 miRNAs that correlates with cancer-specific survival. The two groups share three miRNAs. Importantly, miRNAs that correlate with survival are independent prognostic factors either when considered individually or as signatures. CONCLUSIONS: miRNAs expression associates with TP53 status and with reduced survival after surgical treatment of squamous cell carcinoma of the head and neck.

[64]

**TÍTULO / TITLE:** - Expression of apoptosis regulating proteins identifies stage II and III colon cancer patients with high risk of recurrence.

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

**REVISTA / JOURNAL:** - J Surg Oncol. 2013 Nov 19. doi: 10.1002/jso.23495.

●● Enlace al texto completo (gratis o de pago) [1002/jso.23495](#)

**AUTORES / AUTHORS:** - Belt EJ; Stockmann HB; Delis-van Diemen PM; Bril H; Tijssen M; van Essen HF; Heymans MW; Belien JA; Carvalho B; Cillessen SA; Meijer GA

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands.

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVES: Deregulation of apoptosis related genes may be associated with poor outcome in cancer. Aim of the present study was to investigate the prognostic role of expression levels of apoptosis related proteins in stage II and III colon cancer. METHODS: From tumor samples of 386 stage II and III colon cancer patients, DNA was isolated and tissue microarrays

were constructed. Expression of Bcl-2, Bcl-X, BAX, XIAP, Fas, FasL and c-FLIP was evaluated and PCR-based microsatellite instability analysis was performed. RESULTS: High FasL expressing tumors were associated with high disease recurrence rates in stage II colon cancer patients overall, as was low Bcl-X expression in microsatellite stable stage II patients. In stage II patients, a multivariable model based on FasL and Bcl-XL expression revealed a significant association with disease free survival (DFS). In stage III colon cancer patients, low Bcl-2, low BAX and low Fas expression levels were associated with worse outcome. In these patients a multivariable model based on angiogenesis and Bcl-2, Fas and FasL expression was significantly associated with DFS. CONCLUSIONS: Stage II patients with low Bcl-X and high FasL protein expression levels and stage III patients with low Fas, high FasL and low Bcl-2 expression could be considered as high risk for disease recurrence. J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

[65]

**TÍTULO / TITLE:** - Randomized trial of preoperative docetaxel with or without capecitabine after 4 cycles of 5-fluorouracil-epirubicin-cyclophosphamide (FEC) in early-stage breast cancer: exploratory analyses identify Ki67 as a predictive biomarker for response to neoadjuvant chemotherapy.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Oct 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10549-013-2691-y](#)

**AUTORES / AUTHORS:** - Ohno S; Chow LW; Sato N; Masuda N; Sasano H; Takahashi F; Bando H; Iwata H; Morimoto T; Kamigaki S; Nakayama T; Nakamura S; Kuroi K; Aogi K; Kashiwaba M; Yamashita H; Hisamatsu K; Ito Y; Yamamoto Y; Ueno T; Fakhrejahani E; Yoshida N; Toi M

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [info@ootr-institute.org](mailto:info@ootr-institute.org).

**RESUMEN / SUMMARY:** - This randomized, multicenter study compared the efficacy of docetaxel with or without capecitabine following fluorouracil/epirubicin/cyclophosphamide (FEC) therapy in operable breast cancer and investigated the role of Ki67 as a predictive biomarker. Patients were randomized to 4 cycles of docetaxel/capecitabine (docetaxel: 75 mg/m<sup>2</sup> on day 1; capecitabine: 1,650 mg/m<sup>2</sup> on days 1-14 every 3 weeks) or docetaxel alone (75 mg/m<sup>2</sup> on day 1 every 3 weeks) after completion of 4 cycles of FEC (5-fluorouracil 500 mg/m<sup>2</sup>, epirubicin 100 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> on day 1 every 3 weeks). The primary endpoint was the pathological complete response (pCR) rate. Predictive factor analysis was conducted using clinicopathological markers, including hormone receptors and Ki67 labeling index (Ki67LI). A total of 477 patients were randomized; the overall response in the docetaxel/capecitabine and docetaxel groups was 88.3 and 87.4 %, respectively. There were no significant differences in the pCR rate (docetaxel/capecitabine: 23 %; docetaxel: 24 %; p = 0.748), disease-free survival, or overall survival. However, patients with mid-range Ki67LI (10-20 %) showed a trend towards improved pCR rate with docetaxel/capecitabine compared to docetaxel alone. Furthermore, multivariate logistic regression analysis showed pre-treatment Ki67LI (odds ratio 1.031; 95 % CI 1.014-1.048; p = 0.0004) to be a significant predictor of pCR in this neoadjuvant treatment setting. Docetaxel/capecitabine (after 4 cycles of

FEC) did not generate significant improvement in pCR compared to docetaxel alone. However, exploratory analyses suggested that assessment of pre-treatment Ki67LI may be a useful tool in the identification of responders to preoperative docetaxel/capecitabine in early-stage breast cancer.

[66]

**TÍTULO / TITLE:** - Soluble interleukin-2 receptor level predicts survival in patients with follicular lymphoma treated with CHOP chemotherapy in the rituximab era.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Nov 3.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.850167](#)

**AUTORES / AUTHORS:** - Prochazka V; Papajik T; Faber E; Raida L; Kapitanova Z; Langova K; Prouzova Z; Jarosova M; Indrak K

**RESUMEN / SUMMARY:** - Abstract This study analyzed the prognostic significance of sIL-2Ralpha levels in 100 prospectively enrolled patients with previously untreated follicular lymphoma. It showed that sIL-2Ralpha level  $\geq$  115 pmol/L at the time of treatment initiation correlates with the high FLIPI-2, bulky disease, advanced clinical stage, number of involved lymph nodes, bone marrow involvement and elevated beta-2 microglobulin (B2M) level. When testing all patients, sIL-2Ralpha  $\geq$  115 pmol/L was associated with significantly shorter progression-free (PFS;  $p < 0.03$ , HR 2.04) but not overall (OS;  $p = 0.06$ , HR 2.36) survival rates. Subanalysis of the CHOP+/-rituximab patients showed higher predictive power for both PFS (HR 2.75, 95% CI 1.24-6.11,  $p = 0.01$ ,) and OS (HR 3.33, 95% CI 1.15-9.63,  $p = 0.02$ ,). In the whole population ( $n = 100$ ), only B2M proved a significant univariate predictor ( $p = 0.007$ , HR = 2.8) of the PFS. When testing patients treated with CHOP+/-rituximab, sIL-2Ralpha was found to be the best univariate predictor for PFS among all FLIPI-2 factors (HR = 2.68,  $p = 0.015$ ). Serum IL-2Ralpha levels may help to refine risk assessment in the modern immunotherapy era complementary to FLIPI-2 factors.

[67]

**TÍTULO / TITLE:** - Prognostic factors for recurrence-free survival in patients with HER2-positive early-stage breast cancer treated with adjuvant trastuzumab.

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

**REVISTA / JOURNAL:** - Onkologie. 2013;36(10):554-8. doi: 10.1159/000355156. Epub 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1159/000355156](#)

**AUTORES / AUTHORS:** - Tonyali O; Coskun U; Sener N; Inanc M; Akman T; Ulas A; Yazilitas D; Bal O; Kucukoner M; Yildirim Ozdemir N; Demirci U; Gunaydin Y; Yildiz R; Karaca H; Umit Unal O; Gumus M; Benekli M; Buyukberber S

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, Department of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Turkey.

**RESUMEN / SUMMARY:** - BACKGROUND: The objective of this study was to identify prognostic factors affecting the recurrence-free survival (RFS) in patients who received a 52-week trastuzumab therapy for HER2-positive early stage breast cancer (EBC). PATIENTS AND METHODS: The medical records of all patients with EBC from 10 centers were analyzed. Pathologic and clinical tumor characteristics were evaluated in

424 female patients who received 52 weeks of adjuvant trastuzumab for HER2-positive EBC. Survival was estimated using the Kaplan-Meier method. Univariate analyses of RFS were performed with the log-rank test. Independent prognostic and predictive factors affecting RFS were assessed by Cox regression analysis. RESULTS: Median follow-up time was 33.1 months (range 9.2-75.9 months). 3-year RFS and overall survival were 87 and 97%, respectively. In multivariate analysis, patients aged 70 years or over ( $p = 0.017$ , relative risk (RR) 2.7, 95% confidence interval (CI) 1.19-6.13), patients with > 9 positive lymph nodes ( $p = 0.001$ , RR 2.52, 95% CI 1.42-4.46), and those with progesterone receptor-negative tumors ( $p = 0.006$ , RR 2.33, 95% CI 1.27-4.27) had worse RFS. CONCLUSION: In spite of a 52-week adjuvant trastuzumab treatment, classic poor prognostic factors for invasive EBC remained as such in patients with HER2-positive EBC.

[68]

**TÍTULO / TITLE:** - The validation of estrogen receptor 1 mRNA expression as a predictor of outcome in patients with metastatic non-small cell lung cancer.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 31. doi: 10.1002/ijc.28571.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28571](#)

**AUTORES / AUTHORS:** - Atmaca A; Al-Batran SE; Wirtz RM; Werner D; Zirlik S; Wiest G; Eschbach C; Claas S; Hartmann A; Ficker JH; Jager E; Brueckl WM

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Oncology, Krankenhaus Nordwest, Frankfurt am Main, Germany.

**RESUMEN / SUMMARY:** - The prognostic role of estrogen receptors in lung cancer is not validated. Results from patients with early stage non-small lung cancer patients indicate a prognostic role of estrogen receptor 1 (ESR1) mRNA expression in these patients. Automated RNA extraction from paraffin and RT-quantitative PCR was used for evaluation of tumoral ESR1 and progesterone receptor (PGR) mRNA expression. The test cohort consisted of 31 patients with advanced or metastatic non-small cell lung cancer (NSCLC) patients, treated in a first-line registry trial. For validation, 53 patients from a randomized multicentre first-line study with eligible tumor samples were evaluated. There was no significant correlation of ESR1 expression with clinical characteristics. ESR1 high expression was of significant positive prognostic value in the training set with a median overall survival (OS) of 15.9 versus 6.2 months for high versus low ESR1 expression patients ( $p = 0.0498$ , HR 0.39). This could be confirmed in the validation cohort with a median OS of 10.9 versus 5.0 months in ESR1 high versus low patients, respectively ( $p = 0.0321$ , HR 0.51). In the multivariate analysis adjusted for histological subtype, gender, age and performance status, ESR1 expression remained an independent prognostic parameter for survival in both cohorts. In contrast to ESR1, PGR expression was not able to separate prognostic groups or to predict outcome significantly (for OS;  $p = 0.94$ ). Our study shows that ESR1 mRNA as assessed by qPCR represents a reliable method for detecting ESR1 expression in NSCLC and that ESR1 expression is an independent prognostic factor in metastatic NSCLC.

[69]

**TÍTULO / TITLE:** - Polymorphisms in the UGT1A1 gene predict adverse effects of irinotecan in the treatment of gynecologic cancer in Japanese patients.

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

**REVISTA / JOURNAL:** - J Hum Genet. 2013 Oct 3. doi: 10.1038/jhg.2013.105.

●● Enlace al texto completo (gratis o de pago) [1038/jhg.2013.105](#)

**AUTORES / AUTHORS:** - Hirasawa A; Zama T; Akahane T; Nomura H; Kataoka F; Saito K; Okubo K; Tominaga E; Makita K; Susumu N; Kosaki K; Tanigawara Y; Aoki D

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo, Japan [2] Center for Medical Genetics, School of Medicine, Keio University, Tokyo, Japan.

**RESUMEN / SUMMARY:** - Irinotecan is a key chemotherapeutic drug used to treat many tumors, including cervical and ovarian cancers; however, irinotecan can cause toxicity, particularly in the presence of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene polymorphisms, which are associated with reduced enzyme activity. Here, we investigated the prevalence of three different variants of UGT1A1 (UGT1A1\*6, UGT1A1\*27 and UGT1A1\*28) and their relationships with irinotecan-induced adverse events in patients with gynecologic cancer, who are treated with lower doses of irinotecan than patients with other types of solid tumors. Fifty-three female patients treated with irinotecan and 362 female patients not treated with irinotecan were screened for UGT1A1\*6, UGT1A1\*27 and UGT1A1\*28. Homozygosity for UGT1A1\*6 or heterozygosity for UGT1A1\*6/\*28 was associated with a high risk of severe absolute neutrophil count decrease or diarrhea (odds ratios: 16.03 and 31.33, respectively). In contrast, serum bilirubin levels were not associated with irinotecan toxicity. Homozygosity for UGT1A1\*6/\*6 and heterozygosity for UGT1A1\*6/\*28 were associated with an increased risk of absolute neutrophil count and/or diarrhea in Japanese gynecologic cancer patients, despite the lower doses of irinotecan used in these patients. UGT1A1\*6 and UGT1A1\*28 are potential predictors of severe absolute neutrophil decrease and diarrhea caused by low-dose irinotecan in gynecologic cancer patients. Journal of Human Genetics advance online publication, 3 October 2013; doi:10.1038/jhg.2013.105.

[70]

**TÍTULO / TITLE:** - Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan.

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

**REVISTA / JOURNAL:** - Int J Tuberc Lung Dis. 2013 Dec;17(12):1590-5. doi: 10.5588/ijtld.13.0368.

●● Enlace al texto completo (gratis o de pago) [5588/ijtld.13.0368](#)

**AUTORES / AUTHORS:** - Ke WM; Chen LS; Parng IM; Chen WW; On AW

**INSTITUCIÓN / INSTITUTION:** - Division of Drug Safety, Taiwan Drug Relief Foundation, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - OBJECTIVES: To quantify the incidence of tuberculosis (TB) in rheumatoid arthritis patients undergoing treatment with tumour necrosis factor-alpha inhibitors (TNFi). DESIGN: In a retrospective cohort study conducted using data from Taiwan's National Health Insurance claims databases, rheumatoid arthritis patients notified during the period 2006-2008 were recruited and classified based on types of TNFi treatment received. Active TB was the primary outcome. TB risk was estimated

using Cox's proportional hazard model. The TB screening rate within 30 days of initiating treatment with TNFi was examined. RESULTS: Respectively 5079 and 829 patients were included in the non-TNFi and TNFi groups. Active TB rates were respectively 1411.3 and 679.5 events per 100 000 person-years in patients treated with adalimumab and etanercept. Significant TB risk was noted in patients treated with TNFi (aHR 4.87, 95%CI 2.14-11.06). No significant difference in active TB was observed between the TNFi subgroups (etanercept as reference, aHR 1.89, 95%CI 0.40-6.04). Only 8.7% (n = 9) of TNFi users underwent screening for TB before the first dose of TNFi. CONCLUSIONS: Patients on TNFi have a significantly greater risk of active TB than non-TNFi patients in the Taiwanese population. No difference in TB risk between the two available TNFi groups was noted. Screening for TB before initiating treatment with TNFi should be implemented.

[71]

**TÍTULO / TITLE:** - Transcription Factor STAT3 As a Prognostic Marker and Therapeutic Target in Cancer.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2012.45.6004](#)

**AUTORES / AUTHORS:** - Frank DA

**INSTITUCIÓN / INSTITUTION:** - Dana-Farber Cancer Institute; Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

[72]

**TÍTULO / TITLE:** - Sustained virological response in HIV/HCV co-infected patients treated with pegylated interferon/ribavirin can be predicted from the overall rate of viral load decline over the first 4 weeks of therapy.

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

**REVISTA / JOURNAL:** - J Infect. 2013 Nov 22. pii: S0163-4453(13)00361-7. doi: 10.1016/j.jinf.2013.11.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.jinf.2013.11.009](#)

**AUTORES / AUTHORS:** - Rivero-Juarez A; Neukam K; Labarga P; Camacho A; Macias J; Barreiro P; Torre-Cisneros J; Pineda JA; Soriano V; Rivero A

**INSTITUCIÓN / INSTITUTION:** - Unit of Infectious Diseases, Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC), Hospital Universitario Reina Sofia, Cordoba, España.

**RESUMEN / SUMMARY:** - OBJECTIVE: It is not known whether the probability of achieving sustained virological response (SVR) can be determined on the basis of the magnitude of HCV viral decline over the first 4 weeks of Peg-IFN/RBV treatment of HIV/HCV co-infected patients who fail to achieve a rapid virological response (RVR). METHODS: HIV patients co-infected with HCV genotype 1 naive to Peg-IFN/RBV treatment were included. HCV viral decline from baseline to week 4 was graded. The positive predictive value (PPV) for SVR was evaluated according to the magnitude of HCV viral decline at week 4. RESULTS: One hundred and fifty patients were included. Thirty-four (22.6%) patients achieved RVR, 33 of these (PPV [CI 95%]; 97.05% [86.34-99.85]) achieved SVR. In those patients who did not achieve RVR, the probability to

achieving SVR was graded according to the magnitude of viral decline at week 4 (>2 log<sub>10</sub> [55.5%], >2.5 log<sub>10</sub> [73.3%] and >3 log<sub>10</sub> [75%]). The combination of undetectable and magnitude of decline (>2.5 log<sub>10</sub>) had a PPV for SVR of 89.8% (CI 95%; 0.794-0.964). CONCLUSIONS: The combination of undetectable HCV viral load and magnitude of decline at week 4 has a high PPV for SVR and identified a higher number of potential Peg-IFN/RBV responders.

[73]

**TÍTULO / TITLE:** - No impact of high-dose cytarabine and asparaginase as early intensification with intermediate-risk paediatric acute lymphoblastic leukaemia: results of randomized trial TCCSG study L99-15.

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

**REVISTA / JOURNAL:** - Br J Haematol. 2013 Oct 26. doi: 10.1111/bjh.12632.

●● Enlace al texto completo (gratis o de pago) [1111/bjh.12632](#)

**AUTORES / AUTHORS:** - Kato M; Koh K; Manabe A; Saito T; Hasegawa D; Isoyama K; Kinoshita A; Maeda M; Okimoto Y; Kajiwara M; Kaneko T; Sugita K; Kikuchi A; Tsuchida M; Ohara A

**INSTITUCIÓN / INSTITUTION:** - Department of Haematology/Oncology, Saitama Children's Medical Centre, Saitama, Japan; Department of Paediatrics, the University of Tokyo, Tokyo, Japan.

**RESUMEN / SUMMARY:** - The Tokyo Children's Cancer Study Group conducted a randomized controlled study to evaluate the effect of experimental early intensification using high-dose cytarabine and L-asparaginase in paediatric intermediate-risk (IR) acute lymphoblastic leukaemia (ALL). A total of 310 IR ALL patients were randomized to receive either experimental early intensification (n = 156) or standard early intensification including standard-dose cytarabine arm (n = 154) after induction therapy. The experimental arm consisted of high-dose cytarabine and L-asparaginase, while the standard arm consisted of standard-dose cytarabine, oral 6-mercaptopurine and cyclophosphamide. The probabilities of event-free survival at 8 years in the experimental and standard arms were 72.3 +/- 3.7% and 77.5 +/- 3.5%, respectively (P = 0.32). The 8-year overall survival rates for these two arms were 85.0 +/- 3.0% and 86.9 +/- 2.8%, respectively (P = 0.72). The frequency of infectious events was significantly higher in the experimental arm (66.4%) than in the standard arm (24.6%) (P < 0.001). In conclusion, experimental early intensification including high-dose cytarabine followed by L-asparaginase had no advantage over standard early intensification in paediatric IR ALL patients.

[74]

**TÍTULO / TITLE:** - Metronomic chemotherapy and anti-angiogenesis: can upgraded pre-clinical assays improve clinical trials aimed at controlling tumor growth?

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

**REVISTA / JOURNAL:** - APMIS. 2013 Oct 26. doi: 10.1111/apm.12201.

●● Enlace al texto completo (gratis o de pago) [1111/apm.12201](#)

**AUTORES / AUTHORS:** - Norrby K

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

**RESUMEN / SUMMARY:** - Metronomic chemotherapy, which is continuously administered systemically at close to non-toxic doses, targets the endothelial cells (ECs) that are proliferating during tumor angiogenesis. This leads to harmful effects of an even greatly increased number contiguous tumor cells. Although pre-clinical studies of angiogenesis-related EC features in vitro and of the anti-angiogenic and anti-tumor effects in vivo of metronomic chemotherapy have provided valuable insights, clinical trials with this type of therapy have been less successful in inhibiting tumor growth. One possible reason for the apparent disconnect between the pre-clinical and clinical outcomes is that most of the currently used experimental angiogenesis assays and tumor models are incapable of yielding data that can be translated readily into the clinical setting. Many of the assays used suffer from unintentional artifactual effects, e.g., oxidative stress in vitro, and inflammation in vivo, which reduces the sensitivity and discriminatory power of the assays. Co-treatment with an antioxidant or the inclusion of antioxidants in the vehicle often significantly affects the angiogenesis-modulating outcome of metronomic mono-chemotherapy in vivo. This 'metronomic chemotherapy vehicle factor' merits further study, as do the observations of antagonistic effects following metronomic treatment with a combination of standard chemotherapeutic drugs in vivo.

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[75]

**TÍTULO / TITLE:** - Circulating proteins as potential biomarkers of sunitinib and interferon-alpha efficacy in treatment-naive patients with metastatic renal cell carcinoma.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2333-4](#)

**AUTORES / AUTHORS:** - Harmon CS; Deprimo SE; Figlin RA; Hudes GR; Hutson TE; Michaelson MD; Negrier S; Kim ST; Huang X; Williams JA; Eisen T; Motzer RJ

**INSTITUCIÓN / INSTITUTION:** - Pfizer Oncology, 10646 Science Center Drive, La Jolla, San Diego, CA, 92121, USA.

**RESUMEN / SUMMARY:** - **PURPOSE:** We investigated potential biomarkers of efficacy in a phase III trial of sunitinib versus interferon-alpha (IFN-alpha), first-line in metastatic renal cell carcinoma (mRCC), by analyzing plasma levels of vascular endothelial growth factor (VEGF)-A, VEGF-C, soluble VEGF receptor-3 (sVEGFR-3) and interleukin (IL)-8. **METHODS:** Seven hundred and fifty mRCC patients were randomized to oral sunitinib 50 mg/day in repeated cycles of a 4-week on/2-week off schedule or IFN-alpha 9 million units subcutaneously thrice weekly. Plasma samples collected from a subset of 63 patients on days 1 and 28 of cycles 1-4 and at end of treatment were analyzed by ELISA. **RESULTS:** Baseline characteristics of biomarker-evaluated patients in sunitinib (N = 33) and IFN-alpha (N = 30) arms were comparable to their respective intent-to-treat populations. By univariate Cox regression analysis, low baseline soluble protein levels were associated with lower risk of progression/death (all P < 0.05): in both treatment arms, baseline VEGF-A and IL-8 were associated with overall survival (OS) and baseline VEGF-C with progression-free survival (PFS); in the sunitinib arm, baseline VEGF-A was associated with PFS and baseline sVEGFR-3 with PFS and OS; in the IFN-alpha arm, baseline IL-8 was associated with PFS. In multivariate analysis, baseline sVEGFR-3 and IL-8 remained independent predictors of

OS in the sunitinib arm, while no independent predictors of outcome remained in the IFN-alpha arm. Pharmacodynamic changes were not associated with PFS or OS for any plasma protein investigated. CONCLUSIONS: Our findings suggest that, in mRCC, baseline VEGF-A and IL-8 may have prognostic value, while baseline sVEGFR-3 may predict sunitinib efficacy.

[76]

**TÍTULO / TITLE:** - Differential prognosis of metastatic colorectal cancer patients post-progression to first-line triplet chemotherapy plus bevacizumab, FIr-B/FOx, according to second-line treatment and KRAS genotype.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):17-26. doi: 10.3892/ijo.2013.2179. Epub 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2179](#)

**AUTORES / AUTHORS:** - Bruera G; Cannita K; Giordano AV; Vicentini R; Ficorella C; Ricevuto E

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology, S. Salvatore Hospital, University of L'Aquila, I-67100 L'Aquila, Italy.

**RESUMEN / SUMMARY:** - Clinical outcome post-progression to first-line triplet chemotherapy (CT) plus bevacizumab (FIr-B/FOx) was evaluated in metastatic colorectal cancer (MCRC) patients (pts). Second-line treatment was selected according to fitness, KRAS genotype, previous efficacy and safety. Efficacy was evaluated and compared according to treatment or KRAS genotype, using log-rank analysis. Among 54 pts, median overall survival (OS) post-progression was 12 months, significantly better in 40 (74.1%) treated compared to 14 (25.9%) who died without further treatment. Second-line surgical treatment, 4 pts (7.4%), medical treatment, 36 pts (66.7%): triplet CT plus targeted agent, 10 (18.5%); triplet regimens, 19 (35.2%); doublet/monotherapy, 7 (13%). At follow-up of 14 months, objective response rate (ORR) was 38%, metastasectomies 12.5%, progression-free survival (PFS) 10 months, OS 14 months. According to treatment, ORR, metastasectomies, PFS and OS were significantly favourable in triplet CT plus targeted agent compared to triplet, respectively: 80%, 40%, 13 months, not reached; 28%, 6%, 8 months, 11 months. PFS and OS were significantly worse in c.35 G>A mutant compared to wild-type and/or other mutant patients. Prognosis after progression to firstline FIr-B/FOx may be significantly favourable in MCRC pts re-challenged with intensive regimens, and unfavourable in c.35 G>A KRAS mutant patients.

[77]

**TÍTULO / TITLE:** - Modeling RAS phenotype in colorectal cancer uncovers novel molecular traits of RAS dependency and improves prediction of response to targeted agents in patients.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-](#)

[1943](#)

**AUTORES / AUTHORS:** - Guinney J; Ferte C; Dry JR; McEwen R; Manceau G; Kao K; Chang KM; Bendtsen C; Hudson K; Huang E; Dougherty B; Ducreux M; Soria JC; Friend SH; Derry J; Laurent-Puig P

**INSTITUCIÓN / INSTITUTION:** - Cancer research - Systems Biology, Sage Bionetworks.

**RESUMEN / SUMMARY:** - PURPOSE: KRAS wild-type status is an imperfect predictor of sensitivity to anti-EGFR monoclonal antibodies in colorectal cancer (CRC), motivating efforts to identify novel molecular aberrations driving RAS. This study aimed to build a quantitative readout of RAS pathway activity to: (1) uncover molecular surrogates of RAS activity specific to CRC; (2) improve the prediction of cetuximab response in patients; (3) suggest new treatment strategies. Methods: A model of RAS pathway activity was trained in a large CRC dataset and validated in three independent CRC patient datasets. Novel molecular traits were inferred from the TCGA CRC data. The ability of the RAS model to predict resistance to cetuximab was tested in mouse xenografts and three independent patient cohorts. Drug sensitivity correlations between our model and large cell line compendiums were performed. RESULTS: The performance of the RAS model was remarkably robust across 3 validation datasets. (1) Our model confirmed the heterogeneity of the RAS phenotype in KRAS wild-type patients, and suggests novel molecular traits driving its phenotype (e.g. MED12 loss, GBXW7 mutation, MAP2K4 mutation). (2) It improved the prediction of response and progression free survival (HR=2.0; p<.01) to cetuximab compared to KRAS mutation (xenograft and patient cohorts). (3) Our model consistently predicted sensitivity to MEK inhibitors (p<.01) in 2 cell panel screens. CONCLUSIONS: Modeling the RAS phenotype in CRC allows for the robust interrogation of RAS pathway activity across cell lines, xenografts, and patient cohorts. It demonstrates clinical utility in predicting response to anti-EGFR agents and MEK inhibitors.

[78]

**TÍTULO / TITLE:** - Experimental HBsAg/anti-HBs complex assay for prediction of HBeAg loss in chronic hepatitis B patients treated with peg-interferon and adefovir.

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

**REVISTA / JOURNAL:** - Antivir Ther. 2013 Nov 21. doi: 10.3851/IMP2707.

●● [Enlace al texto completo \(gratis o de pago\) 3851/IMP2707](#)

**AUTORES / AUTHORS:** - de Niet A; Jansen L; Zaaier HL; Klause U; Takkenberg B; Janssen HL; Chu T; Petric R; Reesink HW

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands. [a.deniet@amc.nl](mailto:a.deniet@amc.nl).

**RESUMEN / SUMMARY:** - BACKGROUND: We studied whether HBsAg/anti-HBs immune-complex levels in chronic hepatitis B (CHB) patients receiving anti-viral therapy could be used as a response marker at baseline (BL), or early during treatment to predict treatment outcome. METHODS: An experimental array-based assay (IMPACT - Immunological Multi-Parameter Chip Technology, Roche Diagnostics) served to determine HBsAg, anti-HBs and complex levels. We tested a panel of serum samples of 40 HBeAg-positive and 44 HBeAg-negative patients who received pegylated-interferon and adefovir for 48 weeks. RESULTS: HBsAg loss occurred in 4 of 40 HBeAg-positive and 4 of 44 HBeAg-negative patients. Fourteen of 40 HBeAg positive patients lost HBeAg and 12 of them formed anti-HBe. At BL complexes were present in 83 (99%) patients, whereas free anti-HBs levels were detectable in 5

patients. Complex levels at BL and week 12 were higher in HBeAg-positive patients with HBeAg loss, compared to patients who retained HBeAg ( $p=0.002$  and  $p=0.005$  respectively). ROC analysis for HBeAg loss in HBeAg positive patients at BL and WK 12 showed AUC 0.79 ( $p=0.002$ ) and AUC 0.82 ( $p=0.003$ ) for complex levels. We found no correlation in either HBeAg-positive or -negative patients between complex levels and HBsAg loss. CONCLUSIONS: We demonstrated for the first time that before and during treatment HBsAg/anti-HBs immune-complex levels can predict HBeAg loss in HBeAg-positive CHB patients treated with peg-interferon and adefovir. Complexes were present in almost all patients at BL and were higher in patients who lost HBeAg. In conclusion, determining HBsAg/anti-HBs immune-complex levels before and early during treatment could aid in selecting CHB patients with an optimal chance to achieve HBeAg loss.

[79]

**TÍTULO / TITLE:** - The antiparasitic clioquinol induces apoptosis in leukemia and myeloma cells by inhibiting histone deacetylase activity.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 22;288(47):34181-9. doi: 10.1074/jbc.M113.472563. Epub 2013 Oct 10.

●● [Enlace al texto completo \(gratis o de pago\) 1074/jbc.M113.472563](#)

**AUTORES / AUTHORS:** - Cao B; Li J; Zhu J; Shen M; Han K; Zhang Z; Yu Y; Wang Y; Wu D; Chen S; Sun A; Tang X; Zhao Y; Qiao C; Hou T; Mao X

**INSTITUCIÓN / INSTITUTION:** - From the Cyrus Tang Hematology Center.

**RESUMEN / SUMMARY:** - The antiparasitic clioquinol (CQ) represents a class of novel anticancer drugs by interfering with proteasome activity. In the present study, we found that CQ induced blood cancer cell apoptosis by inhibiting histone deacetylases (HDACs). CQ accumulated the acetylation levels of several key proteins including histone H3 (H3), p53, HSP90, and alpha-tubulin. In the mechanistic study, CQ was found to down-regulate HDAC1, -3, -4, and -5 in both myeloma and leukemia cells. Computer modeling analysis revealed that CQ was well docked into the active pocket of the enzyme, where the oxygen and nitrogen atoms in CQ formed stable coordinate bonds with the zinc ion, and the hydroxyl group from CQ formed an effective hydrogen bond with Asp-267. Moreover, co-treatment with CQ and zinc/copper chloride led to decreased Ac-H3. Furthermore, CQ inhibited the activity of Class I and IIa HDACs in the cell-free assays, demonstrating that CQ interfered with HDAC activity. By inhibiting HDAC activity, CQ induced expression of p21, p27, and p53, cell cycle arrest at G1 phase, and cell apoptosis. This study suggested that the HDAC enzymes are targets of CQ, which provided a novel insight into the molecular mechanism of CQ in the treatment of hematological malignancies.

[80]

**TÍTULO / TITLE:** - Interferon-dependent IL-10 production by Tregs limits tumor Th17 inflammation.

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

**REVISTA / JOURNAL:** - J Clin Invest. 2013 Oct 8. pii: 65180. doi: 10.1172/JCI65180.

●● [Enlace al texto completo \(gratis o de pago\) 1172/JCI65180](#)

**AUTORES / AUTHORS:** - Stewart CA; Metheny H; Iida N; Smith L; Hanson M; Steinhagen F; Leighty RM; Roers A; Karp CL; Muller W; Trinchieri G

**RESUMEN / SUMMARY:** - The capacity of IL-10 and Tregs in the inflammatory tumor microenvironment to impair anticancer Th1 immunity makes them attractive targets for cancer immunotherapy. IL-10 and Tregs also suppress Th17 activity, which is associated with poor prognosis in several cancers. However, previous studies have overlooked their potential contribution to the regulation of pathogenic cancer-associated inflammation. In this study, we investigated the origin and function of IL-10-producing cells in the tumor microenvironment using transplantable tumor models in mice. The majority of tumor-associated IL-10 was produced by an activated Treg population. IL-10 production by Tregs was required to restrain Th17-type inflammation. Accumulation of activated IL-10+ Tregs in the tumor required type I IFN signaling but not inflammatory signaling pathways that depend on TLR adapter protein MyD88 or IL-12 family cytokines. IL-10 production limited Th17 cell numbers in both spleen and tumor. However, type I IFN was required to limit Th17 cells specifically in the tumor microenvironment, reflecting selective control of tumor-associated Tregs by type I IFN. Thus, the interplay of type I IFN, Tregs, and IL-10 is required to negatively regulate Th17 inflammation in the tumor microenvironment. Therapeutic interference of this network could therefore have the undesirable consequence of promoting Th17 inflammation and cancer growth.

[81]

**TÍTULO / TITLE:** - Cancerous Inhibitor of Protein Phosphatase 2A, an Emerging Human Oncoprotein and a Potential Cancer Therapy Target.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Nov 15;73(22):6548-53. doi: 10.1158/0008-5472.CAN-13-1994. Epub 2013 Nov 7.

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

[1994](#)

**AUTORES / AUTHORS:** - Khanna A; Pimanda JE; Westermarck J

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Adult Cancer Program, Lowy Cancer Research Centre and Prince of Wales Hospital, University of New South Wales (UNSW) Medicine; Translational Cancer Research Network, University of New South Wales (UNSW), Sydney, Australia; Turku Centre for Biotechnology, University of Turku and Abo Akademi University; and Department of Pathology, University of Turku, Turku, Finland.

**RESUMEN / SUMMARY:** - Protein phosphatase 2A (PP2A) complexes function as tumor suppressors by inhibiting the activity of several critical oncogenic signaling pathways. Consequently, inhibition of the PP2A phosphatase activity is one of many prerequisites for the transformation of normal human cells into cancerous cells. However, mechanisms for PP2A inactivation in human cancers are poorly understood. The aberrant expression of cancerous inhibitor of protein phosphatase 2A (CIP2A), a recently identified endogenous PP2A inhibitor in malignant cells, is one such mechanism. Various independent studies have validated CIP2A's role in promoting tumor growth and resistance to apoptosis and senescence-inducing therapies. Notably, high CIP2A expression predicts poor patient prognosis in several human cancer types. Among the oncogenic proteins dephosphorylated by PP2A, the MYC oncoprotein,

which is phosphorylated at serine 62, has surfaced as a marker for the oncogenic activity of CIP2A. The positive-feedback loop between CIP2A and MYC augments the activity of MYC in cancer cells. In addition, CIP2A promotes the phosphorylation and activity of additional oncoproteins, including E2F1 and AKT. However, CIP2A is not essential for normal mouse growth and development. These findings indicate that CIP2A is a novel anticancer target based on PP2A reactivation and inhibition of the oncogenic activity of its downstream effectors. The potential approaches and feasibility of targeting CIP2A are discussed here. *Cancer Res*; 73(22); 6548-53. ©2013 AACR.

[82]

**TÍTULO / TITLE:** - Clinical study evaluating the effect of bevacizumab on the severity of zoledronic acid-related osteonecrosis of the jaw in cancer patients.

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

**REVISTA / JOURNAL:** - *Bone*. 2014 Jan;58:103-7. doi: 10.1016/j.bone.2013.10.002. Epub 2013 Oct 9.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.bone.2013.10.002](#)

**AUTORES / AUTHORS:** - Lescaille G; Coudert AE; Baaroun V; Ostertag A; Charpentier E; Javelot MJ; Toledo R; Goudot P; Azerad J; Berdal A; Spano JP; Ruhin B; Descroix V

**INSTITUCIÓN / INSTITUTION:** - Oral Surgery Department, Pitie-Salpetriere University Hospital, Paris Diderot University, Paris, France; UMR CNRS 7211/INSERM 959, Pitie-Salpetriere University Hospital, F-75013 Paris, France. Electronic address: [geraldine.lescaille@gmail.com](mailto:geraldine.lescaille@gmail.com).

**RESUMEN / SUMMARY:** - This study aimed to evaluate the effect of bevacizumab (BVZ) on the severity of osteonecrosis of the jaw (ONJ) in a cohort of cancer patients treated with intravenous zoledronic acid (ZA). We reviewed 42 oncologic patients with ONJ between 2007 and 2010. Only patients with solid tumors and who had received ZA were included. Data analyses included age, sex, underlying disease, ZA and BVZ dosages, dental history and ONJ characteristics. Of the 42 ONJ patients treated with ZA, 10 also received BVZ. In the 10 ZA/BVZ patients, the mean duration of ZA treatment at the time of ONJ diagnosis was 12.4 months (+/-6.8), compared to 22.9 months (+/-4.8) in the 32 patients who received ZA only ( $p < 0.05$ ). Cox's model analysis of the delay to ONJ diagnosis confirmed the impact of BVZ on ONJ diagnosis. In the ZA/BVZ-treated group, 7 (70%) patients developed spontaneous osteonecrosis. Multiple logistic regression analysis showed that ZA/BVZ is associated with increased risk of developing spontaneous ONJ (OR 6.07; 95% CI, [1.3-28.2],  $p < 0.05$ ). And finally, the number of ONJ lesions was increased in the ZA/BVZ-treated group compared to the ZA group ( $p < 0.01$ ). Other clinical conditions as type of tumor (prostate, breast.), cancer severity or other chemotherapy drugs also could be involved in ONJ evolution. However, this study demonstrates for the first time the potential negative influence of BVZ on the incidence and severity of ONJ in patients receiving ZA. Within the study limits, our results suggest that combination ZA/BVZ treatment may possibly predispose to the development of spontaneous and earlier ONJ.

[83]

**TÍTULO / TITLE:** - A phase I study of lapatinib with whole brain radiotherapy in patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer brain metastases.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov;142(2):405-14. doi: 10.1007/s10549-013-2754-0. Epub 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2754-0](#)

**AUTORES / AUTHORS:** - Lin NU; Freedman RA; Ramakrishna N; Younger J; Storniolo AM; Bellon JR; Come SE; Gelman RS; Harris GJ; Henderson MA; Macdonald SM; Mahadevan A; Eisenberg E; Ligibel JA; Mayer EL; Moy B; Eichler AF; Winer EP

**INSTITUCIÓN / INSTITUTION:** - Harvard Medical School, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA, 02215, USA, [nlin@partners.org](mailto:nlin@partners.org).

**RESUMEN / SUMMARY:** - Brain metastases are common in patients with advanced, Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer. We evaluated the maximum tolerated dose (MTD) and feasibility of lapatinib given concurrently with whole brain radiotherapy (WBRT). Eligible patients had (HER2)-positive breast cancer and  $\geq 1$  brain metastasis. Patients received lapatinib 750 mg twice on day one followed by 1000, 1250, or 1500 mg once daily. WBRT (37.5 Gy, 15 fractions) began 1-8 days after starting lapatinib. Lapatinib was continued through WBRT. Following WBRT, patients received trastuzumab 2 mg/kg weekly and lapatinib 1000 mg once daily. The regimen would be considered feasible if  $< 3/27$  pts treated at the MTD experienced a dose-limiting toxicity (DLT). Thirty-five patients were enrolled; 17 % had central nervous disease (CNS) only. During dose escalation, no patients receiving 1,000 or 1,250 mg and two of five patients receiving 1,500 mg experienced DLTs (grade 3 mucositis and rash). Overall, 7/27 patients at 1,250 mg (MTD) had DLTs: grade 3 rash (n = 2), diarrhea (n = 2), hypoxia (n = 1), and grade 4 pulmonary embolus (n = 2). Among 28 evaluable patients, the CNS objective response rate (ORR) was 79 % [95% confidence interval (CI) 59-92 %] by pre-specified volumetric criteria; 46 % remained progression-free (CNS or non-CNS) at 6 months. The study did not meet the pre-defined criteria for feasibility because of toxicity, although the relationship between study treatment and some DLTs was uncertain. Given the high ORR, concurrent lapatinib-WBRT could still be considered for future study with careful safety monitoring.

[84]

**TÍTULO / TITLE:** - Prognostic Impact of Baseline Serum C-Reactive Protein in Metastatic Renal Cell Carcinoma Patients Treated With Sunitinib.

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

**REVISTA / JOURNAL:** - BJU Int. 2013 Oct 8. doi: 10.1111/bju.12494.

●● Enlace al texto completo (gratis o de pago) [1111/bju.12494](#)

**AUTORES / AUTHORS:** - Beuselinck B; Vano YA; Oudard S; Wolter P; De Smet R; Depoorter L; Teghom C; Karadimou A; Zucman-Rossi J; Debruyne PR; Van Poppel H; Joniau S; Lerut E; Strijbos M; Dumez H; Paridaens R; Van Calster B; Schoffski P

**INSTITUCIÓN / INSTITUTION:** - Department of General Medical Oncology and Laboratory for Experimental Oncology, University Hospitals Leuven, Leuven Cancer Institute, KU Leuven, Herestraat 49, 3000 Leuven, Belgium; Inserm U674 Genomique

fonctionnelle des tumeurs solides, Université Paris-5 René Descartes, 27 rue Juliette Dodu, 75010 Paris, France.

**RESUMEN / SUMMARY:** - OBJECTIVE: To evaluate the impact of baseline serum C-reactive protein (CRP) level on outcome in metastatic renal cell carcinoma (mRCC) patients treated with sunitinib. PATIENTS AND METHODS: We reviewed the charts of mRCC patients who started sunitinib as first targeted treatment between 2005 and 2012 in three hospitals in Belgium and France. Collected data included known prognostic factors for mRCC and anatomical location of metastatic sites, response rate (RR), progression-free survival (PFS) and overall survival (OS). RESULTS: 200 eligible patients were identified by retrospective chart review. Median PFS (mPFS) and median OS (mOS) were 12 and 20 months, respectively. We observed a clear impact of baseline CRP-levels on outcome: mPFS was 25 months in the group with baseline CRP <5 mg/l versus 8 months in the group with baseline CRP >5 mg/l (HR 2.48, 95%CI 1.74-3.59). mOS was 50 versus 12 months respectively (HR 3.17, 2.20-4.68). In the group with baseline CRP <5 mg/l, 61% of patients experienced a partial response (PR) compared to 32% of patients in the group with baseline CRP >5 mg/l (difference = 29%, 95% CI 15-42). When adding baseline CRP (with a log-transformation) to the six variables of the IMDC (International Metastatic RCC Database Consortium) model in a multivariable Cox regression model, baseline CRP was independently associated with poor PFS (HR for each doubling in CRP level: 1.14, 1.03-1.26; p=0.01) and OS (HR: 1.29, 1.16-1.43; p<0.0001). Adding baseline CRP to the model increased the c-statistic of PFS at 5 years from 0.63 (0.59-0.68) to 0.69 (0.65-0.73), and the c-statistic of OS at 5 years from 0.65 (0.60-0.69) to 0.70 (0.66-0.74). Patients with elevated baseline CRP-levels have a poor prognosis independent of the IMDC risk group, whereas IMDC favorable risk patients with a low baseline CRP have a very good outcome. CONCLUSION: Baseline serum CRP level is a strong independent parameter linked with RR, PFS and OS in mRCC patients treated with sunitinib.

[85]

**TÍTULO / TITLE:** - Pemphigus foliaceus-like reaction in a patient with chronic myeloid leukemia treated with the tyrosine kinase inhibitors nilotinib and dasatinib.

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

**REVISTA / JOURNAL:** - Int J Dermatol. 2013 Nov 21. doi: 10.1111/j.1365-4632.2012.5728.x.

●● Enlace al texto completo (gratis o de pago) [1111/j.1365-4632.2012.5728.x](#)

**AUTORES / AUTHORS:** - Nuno-Gonzalez A; Dehesa L; Ricotti C; Kerdel F

**INSTITUCIÓN / INSTITUTION:** - Dermatology Unit, Hospital Universitario Fundación Alcorcón (University Hospital Foundation Alcorcón), Madrid, España.

[86]

**TÍTULO / TITLE:** - IFNL3 (IL28B) polymorphism does not predict long-term response to interferon therapy in HBeAg-positive chronic hepatitis B patients.

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

**REVISTA / JOURNAL:** - J Viral Hepat. 2013 Oct 10. doi: 10.1111/jvh.12177.

●● Enlace al texto completo (gratis o de pago) [1111/jvh.12177](https://doi.org/10.1111/jvh.12177)

**AUTORES / AUTHORS:** - Zhang Q; Lapalus M; Asselah T; Laouenan C; Moucari R; Martinot-Peignoux M; Bieche I; Estrabaud E; De Muynck S; Boyer N; Bedossa P; Vidaud M; Marcellin P; Lada O

**INSTITUCIÓN / INSTITUTION:** - Service d'Hépatologie and Univ Paris Diderot, Sorbonne Paris Cité, CRB3, UMR 773, Inserm, Clichy, France.

**RESUMEN / SUMMARY:** - The impact of IFNL3 (IL28B) polymorphism on response to interferon (IFN) treatment in patients infected with hepatitis B virus (HBV) is controversial. We aimed to investigate whether IFNL3 polymorphism (rs12979860) influences the long-term response of chronic hepatitis B (CHB) treatment to conventional IFN. Design: Ninety-seven HBeAg-positive patients treated with IFN were evaluated in this study. Associations were investigated between IFNL3 genotypes and (i) HBeAg seroconversion at the end of treatment (EOT), (ii) sustained virological response (SVR) and (iii) HBsAg seroconversion through long-term follow-up (LTFU). Patients were followed for a median of 14 years. The majority of patients were infected with HBV genotype A (69.6%) and were Caucasian (77.9%). Ninety-five patients were genotyped at rs12979860. Similar IFNL3 distribution was observed among the different ethnicities ( $P = 0.62$ ) or across HBV genotypes A through G ( $P = 0.70$ ). Thirty-six patients experienced HBeAg seroconversion at EOT; HBeAg seroconversion rates were 37.0 and 35.5% in patients with CC and CT/TT genotypes, respectively ( $P = 0.82$ ). Among the 44 patients (45%) who achieved a SVR, SVR rates were 48.9 and 39.6% in patients with CC and CT/TT IL28B genotypes, respectively ( $P = 0.80$ ). HBsAg seroconversion occurred through LTFU in 28 patients. HBsAg seroconversion rates were 25.5 and 31.2% in patients with CC and CT/TT genotypes, respectively ( $P = 0.51$ ). No significant relationship between IFNL3 rs12979860 and fibrosis stage was observed ( $P = 0.85$ ). IFNL3 genotype was neither associated with SVR, nor with HBeAg seroconversion and long-term HBsAg seroconversion in HBeAg-positive CHB patients responding to IFN therapy.

[87]

**TÍTULO / TITLE:** - Endothelium-mediated survival of leukemic cells and angiogenesis-related factors are affected by lenalidomide treatment in chronic lymphocytic leukemia.

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

**REVISTA / JOURNAL:** - Exp Hematol. 2013 Nov 6. pii: S0301-472X(13)00816-3. doi: 10.1016/j.exphem.2013.10.007.

●● Enlace al texto completo (gratis o de pago) [1016/j.exphem.2013.10.007](https://doi.org/10.1016/j.exphem.2013.10.007)

**AUTORES / AUTHORS:** - Maffei R; Fiorcari S; Bulgarelli J; Rizzotto L; Martinelli S; Rigolin GM; Debbia G; Castelli I; Bonacorsi G; Santachiara R; Forconi F; Rossi D; Laurenti L; Palumbo GA; Vallisa D; Cuneo A; Gaidano G; Luppi M; Marasca R

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy. Electronic address: [rossana.maffei@unimore.it](mailto:rossana.maffei@unimore.it).

**RESUMEN / SUMMARY:** - Lenalidomide is an IMiD® immunomodulatory agent clinically active in chronic lymphocytic leukemia (CLL) patients. We evaluated the activity of lenalidomide inside an in vitro co-culture system of endothelial and CLL cells. Lenalidomide was able to inhibit CLL survival advantage mediated by endothelial contact. Moreover, the marked increase of in vitro angiogenesis determined by CLL-

derived conditioned media was reduced by lenalidomide. We also analyzed peripheral blood collected from 27 relapsed/refractory CLL patients being treated with lenalidomide within a Phase II trial. Plasma levels of VEGF and THBS-1 decreased whereas Ang2 and Ang increased during treatment. Patients who respond to lenalidomide showed a more pronounced decrease of VEGF and bFGF than patients with stable or progressive disease ( $p=0.007$  and  $p=0.005$ ). Furthermore, lenalidomide reduced circulating endothelial cells and endothelial progenitors by increasing the percentage of apoptotic cells. Conversely, for 6 matched bone marrow biopsies available before and after treatment, we did not detect any modification in vessel density, suggesting a possible mechanism of vessel normalization rather than regression. In conclusion, our study provides further evidence that the anti-CLL effect of lenalidomide is mediated through the alteration of microenvironmental elements, implying the modulation of several angiogenesis-related factors and disruption of CLL cross-talk with endothelial cells.

[88]

**TÍTULO / TITLE:** - Plasma homocysteine, methionine and S-adenosylhomocysteine levels following high-dose methotrexate treatment in pediatric patients with acute lymphoblastic leukemia or Burkitt lymphoma: association with hepatotoxicity.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Nov 14.

●● [Enlace al texto completo \(gratis o de pago\) 3109/10428194.2013.850684](#)

**AUTORES / AUTHORS:** - Kubota M; Nakata R; Adachi S; Watanabe KI; Heike T; Takeshita Y; Shima M

**INSTITUCIÓN / INSTITUTION:** - Department of Human Life and Environment, Nara Women's University, Nara, Japan.

**RESUMEN / SUMMARY:** - This study aimed to investigate: (i) changes of plasma homocysteine, methionine and S-adenosylhomocysteine levels following high-dose methotrexate (HD-MTX) treatment and (ii) the correlation of these sulfur-containing amino acids with MTX-induced hepatotoxicity. Fifteen pediatric patients with acute lymphoblastic leukemia and one patient with Burkitt lymphoma, with a total of 26 treatment courses of HD-MTX, were enrolled. Homocysteine levels increased at 24 h after HD-MTX treatment, and showed marginal decreases at 48 and 72 h. Methionine levels showed a biphasic pattern, i.e. an initial decrease at 24 h followed by increases at 48 and 72 h. S-adenosylhomocysteine exhibited a marginal decrease at 24 h. Changes of homocysteine exhibited significant correlation only with a maximum increase of alanine aminotransferase or total bilirubin from baseline. This study has demonstrated, for the first time, simultaneous changes of plasma homocysteine, methionine and S-adenosylhomocysteine following HD-MTX. The potential of homocysteine as a marker of hepatotoxicity is also presented.

[89]

**TÍTULO / TITLE:** - Lapatinib versus placebo added to Paclitaxel in first-line human epidermal growth factor receptor 2-positive metastatic breast cancer: ethical lessons not learned from Africa.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 20;31(33):4271. doi: 10.1200/JCO.2013.51.0289. Epub 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2013.51.0289](https://doi.org/10.1200/JCO.2013.51.0289)

**AUTORES / AUTHORS:** - Ades F

**INSTITUCIÓN / INSTITUTION:** - Universite Libre de Bruxelles, Brussels, Belgium.

[90]

**TÍTULO / TITLE:** - Validation of the prognostic relevance of plasma C-reactive protein levels in soft-tissue sarcoma patients.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 29;109(9):2316-22. doi: 10.1038/bjc.2013.595. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.595](https://doi.org/10.1038/bjc.2013.595)

**AUTORES / AUTHORS:** - Szkandera J; Gerger A; Liegl-Atzwanger B; Absenger G; Stotz M; Samonigg H; Maurer-Ertl W; Stojakovic T; Ploner F; Leithner A; Pichler M

**INSTITUCIÓN / INSTITUTION:** - Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Graz, Austria.

**RESUMEN / SUMMARY:** - Background:The concept of the involvement of systemic inflammation in cancer progression and metastases has gained attraction within the past decade. C-reactive protein (CRP), a non-specific blood-based marker of the systemic inflammatory response, has been associated with decreased survival in several cancer types. The aim of the present study was to validate the prognostic value of pre-operative plasma CRP levels on clinical outcome in a large cohort of soft-tissue sarcoma (STS) patients. Methods:Three hundred and four STS patients, operated between 1998 and 2010, were retrospectively evaluated. CRP levels and the impact on cancer-specific survival (CSS), disease-free survival (DFS) and overall survival (OS) were assessed using Kaplan-Meier curves and univariate as well as multivariate Cox proportional models. Additionally, we developed a nomogram by supplementing the plasma CRP level to the well-established Kattan nomogram and evaluated the improvement of predictive accuracy of this novel nomogram by applying calibration and Harrell's concordance index (c-index). Results:An elevated plasma CRP level was significantly associated with established prognostic factors, including age, tumour grade, size and depth ( $P<0.05$ ). In multivariate analysis, increased CRP levels were significantly associated with a poor outcome for CSS (HR=2.05; 95% CI=1.13-3.74;  $P=0.019$ ) and DFS (HR=1.88; 95% CI=1.07-3.34;  $P=0.029$ ). The estimated c-index was 0.74 using the original Kattan nomogram and 0.77 when the plasma CRP level was added. Conclusion:An elevated pre-operative CRP level represents an independent prognostic factor that predicts poor prognosis and improves the predictive ability of the Kattan nomogram in STS patients. Our data suggest to further prospectively validate its potential utility for individual risk stratification and clinical management of STS patients.

[91]

**TÍTULO / TITLE:** - Angiogenesis inhibitor therapies for advanced renal cell carcinoma: Toxicity and treatment patterns in clinical practice from a global medical chart review.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):5-16. doi: 10.3892/ijo.2013.2181. Epub 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2181](https://doi.org/10.3892/ijo.2013.2181)

**AUTORES / AUTHORS:** - Oh WK; McDermott D; Porta C; Levy A; Elaidi R; Scotte F; Hawkins R; Castellano D; Bellmunt J; Rha SY; Sun JM; Nathan P; Feinberg BA; Scott J; McDermott R; Ahn JH; Wagstaff J; Chang YH; Ou YC; Donnellan P; Huang CY; McCaffrey J; Chiang PH; Chuang CK; Korves C; Neary MP; Diaz JR; Mehmud F; Duh MS

**INSTITUCIÓN / INSTITUTION:** - Dana-Farber Cancer Institute, Boston, MA, USA.

**RESUMEN / SUMMARY:** - The aim of this study was to assess the treatment patterns and safety of sunitinib, sorafenib and bevacizumab in real-world clinical settings in US, Europe and Asia. Medical records were abstracted at 18 community oncology clinics in the US and at 21 tertiary oncology centers in US, Europe and Asia for 883 patients  $\geq 18$  years who had histologically/cytologically confirmed diagnosis of advanced RCC and received sunitinib (n=631), sorafenib (n=207) or bevacizumab (n=45) as firstline treatment. No prior treatment was permitted. Data were collected on all adverse events (AEs) and treatment modifications, including discontinuation, interruption and dose reduction. Treatment duration was estimated using Kaplan-Meier analysis. Demographics were similar across treatment groups and regions. Median treatment duration ranged from 6.1 to 10.7 months, 5.1 to 8.5 months and 7.5 to 9.8 months for sunitinib, sorafenib and bevacizumab patients, respectively. Grade  $\geq 3$  AEs were experienced by 26.0, 28.0 and 15.6% of sunitinib, sorafenib and bevacizumab patients, respectively. Treatment discontinuations occurred in 62.4 (Asia) to 63.1% (US) sunitinib, 68.8 (Asia) to 90.0% (Europe) sorafenib, and 66.7 (Asia) to 81.8% (US) bevacizumab patients. Globally, treatment modifications due to AEs occurred in 55.1, 54.2 and 50.0% sunitinib, sorafenib and bevacizumab patients, respectively. This study in a large, global cohort of advanced RCC patients found that angiogenesis inhibitors are associated with high rates of AEs and treatment modifications. Findings suggest an unmet need for more tolerable agents for RCC treatment.

[92]

**TÍTULO / TITLE:** - The Germline BIM Deletion Polymorphism Is Not Associated with the Treatment Efficacy of Sorafenib in Patients with Advanced Hepatocellular Carcinoma.

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

**REVISTA / JOURNAL:** - Oncology. 2013;85(5):312-6. doi: 10.1159/000356019. Epub 2013 Nov 9.

●● Enlace al texto completo (gratis o de pago) [1159/000356019](https://doi.org/10.1159/000356019)

**AUTORES / AUTHORS:** - Shao YY; Chang YL; Huang CY; Hsu CH; Cheng AL

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, ROC.

**RESUMEN / SUMMARY:** - Objectives: A germline BIM deletion polymorphism has been proposed to predict a poor treatment efficacy of certain kinase inhibitors. The current study aimed to explore whether the BIM deletion polymorphism predicts the treatment efficacy of sorafenib for advanced hepatocellular carcinoma (HCC). Methods: All patients who were enrolled in clinical trials to receive sorafenib-containing regimens as first-line therapy for advanced HCC and consented to providing peripheral blood samples were included. Polymerase chain reaction followed by gel electrophoresis

was used to detect the germline BIM deletion polymorphism. Results: A total of 89 patients were enrolled; 69 (77%) patients had chronic hepatitis B infection, and 18 (20%) had chronic hepatitis C infection. The heterozygous BIM deletion polymorphism was identified in 9 (10%) patients. Patients with and without the BIM deletion polymorphism had similar response rates (11 vs. 6%) and disease control rates (56 vs. 61%). The time to progression, progression-free survival, and overall survival were similar between patients with and without the BIM deletion polymorphism. After adjusting for basic clinicopathologic variables and treatment regimens, the BIM polymorphism still could not predict treatment outcomes. Conclusions: The BIM deletion polymorphism was not associated with the treatment efficacy of sorafenib for advanced HCC. © 2013 S. Karger AG, Basel.

[93]

**TÍTULO / TITLE:** - Prognostic value of tumor volume for patients with nasopharyngeal carcinoma treated with concurrent chemotherapy and intensity-modulated radiotherapy.

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

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1542-x](#)

**AUTORES / AUTHORS:** - Wu Z; Su Y; Zeng RF; Gu MF; Huang SM

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Tumor Hospital, Xiangya School of Medicine, Central South University, Changsha, 410013, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: We aimed to analyze prognostic factors in patients with nasopharyngeal carcinoma (NPC) treated with concurrent chemotherapy and intensity-modulated radiotherapy (IMRT); in addition, we aimed to elucidate the value of primary gross tumor volume (GTVp) in predicting prognosis of patients. METHODS: Between February 2001 and December 2008, 321 patients with NPC treated with concurrent chemotherapy and IMRT were analyzed retrospectively. GTVp was calculated from treatment planning computed tomography scans. A receiver operating characteristics (ROC) curve was used to determine the best cutoff point of GTVp. RESULTS: The 5-year local failure-free survival (LFFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) for NPC patients were 93.8, 80.1, 73.0, and 83.7 %, respectively. Univariate and multivariate analyses indicated that GTVp had exhibited a statistically significant correlation with LFFS, DMFS, DFS, and OS ( $P < 0.05$ , all), whereas T classification was not an independent prognostic factor. According to ROC curve analysis, 49 and 19 mL were determined as the cutoff points of GTVp for local control and distant metastasis, respectively. Based on this, 321 patients were divided into three volume subgroups. LFFS, DMFS, DFS, and OS demonstrated significant differences among patients in different volume subgroups ( $P < 0.001$ , all) and were superior to T classification for predicting prognosis of NPC patients. CONCLUSIONS: Primary gross tumor volume is an independent prognostic factor in local control, distant metastasis, disease-free survival, and overall survival in NPC. An adjusted TNM staging system that includes GTVp as a quantitative indicator to evaluate prognosis is warranted.

[94]

**TÍTULO / TITLE:** - A Soluble Fragment of the Tumor Antigen BCL2-associated Athanogene 6 (BAG-6) Is Essential and Sufficient for Inhibition of NKp30 Receptor-dependent Cytotoxicity of Natural Killer Cells.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 29;288(48):34295-303. doi: 10.1074/jbc.M113.483602. Epub 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.483602](#)

**AUTORES / AUTHORS:** - Binici J; Hartmann J; Herrmann J; Schreiber C; Beyer S; Guler G; Vogel V; Tumulka F; Abele R; Mantele W; Koch J

**INSTITUCIÓN / INSTITUTION:** - From the Georg-Speyer-Haus, Institute for Biomedical Research, D-60596 Frankfurt am Main and.

**RESUMEN / SUMMARY:** - Immunosurveillance of tumor cells depends on NKp30, a major activating receptor of human natural killer (NK) cells. The human BCL2-associated athanogene 6 (BAG-6, also known as BAT3; 1126 amino acids) is a cellular ligand of NKp30. To date, little is known about the molecular details of this receptor ligand system. Within the current study, we have located the binding site of NKp30 to a sequence stretch of 250 amino acids in the C-terminal region of BAG-6 (BAG-6686-936). BAG-6686-936 forms a noncovalent dimer of 57-59 kDa, which is sufficient for high affinity interaction with NKp30 (KD < 100 nm). As our most important finding, BAG-6686-936 inhibits NKp30-dependent signaling, interferon-gamma release, and degranulation of NK cells in the presence of malignantly transformed target cells. Based on these data, we show for the first time that BAG-6686-936 comprises a subdomain of BAG-6, which is sufficient for receptor docking and inhibition of NKp30-dependent NK cell cytotoxicity as part of a tumor immune escape mechanism. These molecular insights provide an access point to restore tumor immunosurveillance by NK cells and to increase the efficacy of cellular therapies.

[95]

**TÍTULO / TITLE:** - Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Dec 1;119(23):4137-44. doi: 10.1002/cncr.28347. Epub 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28347](#)

**AUTORES / AUTHORS:** - Karagkounis G; Torbenson MS; Daniel HD; Azad NS; Diaz LA Jr; Donehower RC; Hirose K; Ahuja N; Pawlik TM; Choti MA

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland.

**RESUMEN / SUMMARY:** - BACKGROUND: Molecular biomarkers offer the potential for refining prognostic determinants in patients undergoing cancer surgery. Among patients with colorectal cancer, KRAS and BRAF are important biomarkers, but their role in patients undergoing surgical therapy for liver metastases is unknown. In this study, the incidence and prognostic significance of KRAS and BRAF mutations were determined in patients undergoing surgical therapy of colorectal liver metastases (CRLM). METHODS: KRAS and BRAF analysis was performed on 202 patients undergoing surgery for CRLM between 2003 and 2008. Tumor samples were analyzed

for somatic mutations using sequencing analysis (KRAS, codon12/13, BRAF, V600E). The frequency of mutations was ascertained, and their impact on outcome was determined relative to other clinicopathologic factors. RESULTS: KRAS gene mutations were detected in 58/202 patients (29%). In contrast, mutation in the BRAF gene was identified in very low frequency in this surgical cohort, found in only 4/202 (2%) patients. On multivariate analysis, KRAS mutation was associated with worse survival (hazard ratio [HR], 1.99; 95% confidence interval [CI], 1.21-3.26), as well as recurrence risk (HR, 1.68; 95% CI, 1.04-2.70). Although other clinicopathologic features, including tumor number, carcinoembryonic antigen, and primary stage were also associated with survival, KRAS status remained independently predictive of outcome. The low incidence of BRAF mutation limited assessment of its prognostic impact. CONCLUSION: Whereas KRAS mutations were found in approximately one third of patients, BRAF mutations were found in only 2% of patients undergoing surgery for CRLM. KRAS status was an independent predictor of overall and recurrence-free survival. Molecular biomarkers such as KRAS may help to refine our prognostic assessment of patients undergoing surgical therapy for CRLM. Cancer 2013;119:4137-4144. ©2013 American Cancer Society.

[96]

**TÍTULO / TITLE:** - Loss of Special AT-Rich Sequence-Binding Protein 1 (SATB1) Predicts Poor Survival in Patients with Colorectal Cancer.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Oct 1. doi: 10.1111/his.12295.

●● [Enlace al texto completo \(gratis o de pago\) 1111/his.12295](#)

**AUTORES / AUTHORS:** - Al-Sohaily S; Henderson C; Selinger C; Pangon L; Segelov E; Kohonen-Corish M; Warusavitarne J

**INSTITUCIÓN / INSTITUTION:** - Cancer Research Program, Garvan Institute of Medical Research, NSW, Australia; Department of Gastroenterology, Campbelltown and Fairfield Hospitals, NSW, Australia; South Western Sydney Clinical School, University of NSW, Australia.

**RESUMEN / SUMMARY:** - AIM: Special AT-rich sequence-binding protein 1 (SATB1) is a cell type specific matrix attachment region binding protein, functioning as a global genome organizer. This study aims to investigate the expression pattern and the prognostic value of SATB1 in colorectal cancer. METHODS: Prospectively collected data were obtained and tissue microarrays were constructed from a cohort of 352 patients. SATB1 protein expression was evaluated by immunohistochemistry and scored by two independent investigators. RESULTS: SATB1 expression was predominantly nuclear in both normal and cancer tissues. Loss of SATB1 nuclear expression was seen in 22% of colorectal cancers compared to 1.5% of adjacent normal colorectal tissue, and was associated with worse overall survival (P=0.02) independent of age and stage of disease (HR 2.48 with 95% CI 1.31-4.70). Loss of SATB1 expression was more evident in younger patients (P=0.03), tumours with mucinous or signet ring histology (P=0.0001), and poor differentiation (P=0.005). SATB1 expression was associated with a survival advantage in patients with Dukes C tumours who received adjuvant chemotherapy. CONCLUSION: Loss of SATB1 nuclear expression correlates with poor survival and a less favorable response to adjuvant chemotherapy in colorectal cancer. The value of SATB1 in individualized colorectal

cancer therapy warrants further evaluation. This article is protected by copyright. All rights reserved.

[97]

**TÍTULO / TITLE:** - Predictive and prognostic value of early response assessment using 18FDG-PET in advanced non-small cell lung cancer patients treated with erlotinib.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2356-x](#)

**AUTORES / AUTHORS:** - Tiseo M; Ippolito M; Scarlattei M; Spadaro P; Cosentino S; Latteri F; Ruffini L; Bartolotti M; Bortesi B; Fumarola C; Caffarra C; Cavazzoni A; Alfieri RR; Petronini PG; Bordonaro R; Bruzzi P; Ardizzoni A; Soto Parra HJ

**INSTITUCIÓN / INSTITUTION:** - Oncologia Medica, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci 14, 43100, Parma, Italy, [mtiseo@ao.pr.it](mailto:mtiseo@ao.pr.it).

**RESUMEN / SUMMARY:** - BACKGROUND: [18F]fluorodeoxyglucose (FDG)-PET is being evaluated as a tool for the early detection of response to various targeted agents in solid tumors. The aim of this study was to evaluate the predictive value of PET response after 2 days of erlotinib in unselected pretreated patients with stage IV NSCLC. PATIENTS AND METHODS: FDG-PET/CT scans were conducted at baseline and after 2 days of erlotinib, with a CT evaluation performed at baseline and after 45-60 days of therapy. PET responses were evaluated by quantitative changes on SUVmax tumor/non-tumor ratio and classified according to EORTC criteria. PET responses were compared with RECIST responses and related to progression-free (PFS) and overall (OS) survival. Erlotinib effects on glucose uptake were also studied in a panel of NSCLC cell lines. RESULTS: Fifty-three patients were enrolled. At 2 days of erlotinib, 20 (38 %) patients showed partial metabolic response (PMR), 25 (47 %) had stable metabolic disease (SMD) and 8 (15 %) had progressive metabolic disease (PMD). All patients with PMD had confirmed RECIST progression at 45-60 days. Patients with early PMR and SMD had significantly longer PFS ( $p < 0.001$  and  $p = 0.001$ , respectively) and OS ( $p = 0.001$  for both) than PMD patients. CONCLUSIONS: FDG-PET assessment after 2 days of erlotinib could be useful to identify early resistant patients and to predict survival in unselected NSCLC pretreated population.

[98]

**TÍTULO / TITLE:** - A relative ordering-based predictor for tamoxifen-treated estrogen receptor-positive breast cancer patients: multi-laboratory cohort validation.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov 20.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2767-8](#)

**AUTORES / AUTHORS:** - Zhou X; Li B; Zhang Y; Gu Y; Chen B; Shi T; Ao L; Li P; Li S; Liu C; Guo Z

**INSTITUCIÓN / INSTITUTION:** - Bioinformatics Centre, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China.

**RESUMEN / SUMMARY:** - Current predictors for estrogen receptor-positive (ER-positive) breast cancer patients receiving tamoxifen are often invalid in inter-laboratory

validation. We aim to develop a robust predictor based on the relative ordering of expression measurement (ROE) in gene pairs. Using a large integrated dataset of 420 normal controls and 1,129 ER-positive breast tumor samples, we identified the gene pairs with stable ROEs in normal control and significantly reversed ROEs in ER-positive tumor. Using these gene pairs, we characterized each sample of a cohort of 292 ER-positive patients who received tamoxifen monotherapy for 5 years and then identified relapse risk-associated gene pairs. We extracted a gene pair subset that resulted in the largest positive and negative predictive values for predicting 10-year relapse-free survival (RFS) using a genetic algorithm. A predictor was developed based on the gene pair subset and was validated in 2 large multi-laboratory cohorts (N = 250 and 248, respectively) of ER-positive patients who received 5-year tamoxifen alone. In the first validation cohort, the patients predicted to be tamoxifen sensitive had a 10-year RFS of 91 % (95 % confidence interval [CI] 85-97 %) with an absolute risk reduction of 34 % (95 % CI 17-51 %). The patients predicted to be tamoxifen insensitive had a significantly higher relapse risk than the patients predicted to be tamoxifen sensitive (hazard ratio = 4.99, 95 % CI 2.45-10.17, P = 9.13 x 10<sup>-7</sup>). Similar performance was achieved for the second validation cohort. The predictor performed well in both node-negative and node-positive subsets and added significant predictive power to the clinical parameters. In contrast, 2 previously proposed predictors did not achieve significantly better performances than the baselines of the validation cohorts. In summary, the proposed predictor can accurately and robustly predict tamoxifen sensitivity of ER-positive breast cancer patients and identified patients with a high probability of 10-year RFS following tamoxifen monotherapy.

[99]

**TÍTULO / TITLE:** - Tolerability and efficacy of pegylated interferon-alpha-2a in combination with imatinib for patients with chronic-phase chronic myeloid leukemia.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Sep 16. doi: 10.1002/cncr.28328.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28328](#)

**AUTORES / AUTHORS:** - Johnson-Ansah H; Guilhot J; Rousselot P; Rea D; Legros L; Rigal-Huguet F; Nicolini FE; Mahon FX; Preudhomme C; Guilhot F

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Cote de Nacre University Medical Center, Caen, France.

**RESUMEN / SUMMARY:** - BACKGROUND: The pegylated form of interferon-alpha-2a (PegIFN $\alpha$ 2a) in combination with imatinib has demonstrated a molecular improvement in patients with chronic-phase chronic myeloid leukemia. However, to the authors' knowledge, the appropriate dose of PegIFN $\alpha$ 2a has not been established to date.

**METHODS:** In the French SPIRIT trial, the authors compared 2 initial doses of PegIFN $\alpha$ 2a, taking into account an amendment that recommended reducing that dose from 90 mug/week to 45 mug/week because of toxicities. Accordingly, 2 subgroups of patients were identified: the PegIFN90 group (171 patients who were treated with the 90-mug/week dose) and the PegIFN45 group (50 patients who were treated with the 45-mug/week dose). Both groups were compared for toxicity and efficacy. **RESULTS:** PegIFN $\alpha$ 2a at a dose of 90 mug/week resulted in a rate of 54% of grade 3 to 4 hematologic toxicity compared with 27% with the dose of 45 mug/week (P < .001), leading to discontinuation rates of 40% and 10%, respectively, before 6 months. The

dose reduction did not significantly affect the efficacy of the combination. By 12 months, the cumulative molecular response rates (ie, BCR-ABL/abl  $\leq$  0.01 [IS: molecular responses graded as molecular response 4 (MR4)]) were 14% and 25%, respectively, for the subgroup treated with imatinib at a dose of 400 mg and the PegIFN90 subgroup. After the amendment, the MR4 rates were 10% and 28%, respectively, for the subgroup treated with imatinib at the 400-mg dose and PegIFN45 subgroup ( $P < .0001$ ). CONCLUSIONS: The results of the current study demonstrate that in combination with imatinib, the efficient dose of PegIFNa2a appears to be 45 mug/week. Cancer 2013. © 2013 American Cancer Society.

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[100]

**TÍTULO / TITLE:** - MET and AXL inhibitor NPS-1034 exerts efficacy against lung cancer cells resistant to EGFR kinase inhibitors due to MET or AXL activation.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Oct 28.

- Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-1103](#)

**AUTORES / AUTHORS:** - Rho JK; Choi YJ; Kim SY; Kim TW; Choi EK; Yoon SJ; Park BM; Park E; Bae JH; Choi CM; Lee JC

**INSTITUCIÓN / INSTITUTION:** - Oncology, Asan Medical Center.

**RESUMEN / SUMMARY:** - In non-small cell lung cancer (NSCLC) with EGFR mutations, acquired resistance to EGFR kinase inhibitors (EGFR-TKIs) can occur through generation of bypass signals such as MET or AXL activation. In this study, we investigated the antitumor activity of NPS-1034, a newly developed drug that targets both MET and AXL, in NSCLC cells with acquired resistance to gefitinib or erlotinib (HCC827/GR and HCC827/ER, respectively). Characterization of H820 cells and evaluation of NPS-1034 efficacy in these cells were also performed. The resistance of HCC827/GR was mediated by MET activation, whereas AXL activation led to resistance in HCC827/ER. The combination of gefitinib or erlotinib with NPS-1034 synergistically inhibited cell proliferation and induced cell death in both resistant cell lines. Accordingly, suppression of Akt was noted only in the presence of treatment with both drugs. NPS-1034 was also effective in xenograft mouse models of HCC827/GR. Although the H820 cell line was reported previously to have T790M and MET amplification, we discovered that AXL was also activated in this cell line. There were no antitumor effects of siRNA or inhibitors specific for EGFR or MET, whereas combined treatment with AXL siRNA or NPS-1034 and EGFR-TKIs controlled H820 cells, suggesting that AXL is the main signal responsible for resistance. In addition, NPS-1034 inhibited cell proliferation as well as ROS1 activity in HCC78 cells with ROS1-rearrangement. Our results establish the efficacy of NPS-1034 in NSCLC cells rendered resistant to EGFR-TKIs due to MET or AXL activation or ROS1 rearrangement.

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[101]

**TÍTULO / TITLE:** - Chromosome missegregation rate predicts whether aneuploidy will promote or suppress tumors.

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

**REVISTA / JOURNAL:** - Proc Natl Acad Sci U S A. 2013 Oct 29;110(44):E4134-41. doi: 10.1073/pnas.1317042110. Epub 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1073/pnas.1317042110](https://doi.org/10.1073/pnas.1317042110)

**AUTORES / AUTHORS:** - Silk AD; Zasadil LM; Holland AJ; Vitre B; Cleveland DW; Weaver BA

**INSTITUCIÓN / INSTITUTION:** - Ludwig Institute for Cancer Research and Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, CA 92093.

**RESUMEN / SUMMARY:** - Aneuploidy, a chromosome content other than a multiple of the haploid number, is a common feature of cancer cells. Whole chromosomal aneuploidy accompanying ongoing chromosomal instability in mice resulting from reduced levels of the centromere-linked motor protein CENP-E has been reported to increase the incidence of spleen and lung tumors, but to suppress tumors in three other contexts. Exacerbating chromosome missegregation in CENP-E(+/-) mice by reducing levels of another mitotic checkpoint component, Mad2, is now shown to result in elevated cell death and decreased tumor formation compared with reduction of either protein alone. Furthermore, we determine that the additional contexts in which increased whole-chromosome missegregation resulting from reduced CENP-E suppresses tumor formation have a preexisting, elevated basal level of chromosome missegregation that is exacerbated by reduction of CENP-E. Tumors arising from primary causes that do not generate chromosomal instability, including loss of the INK4a tumor suppressor and microsatellite instability from reduction of the DNA mismatch repair protein MLH1, are unaffected by CENP-E-dependent chromosome missegregation. These findings support a model in which low rates of chromosome missegregation can promote tumorigenesis, whereas missegregation of high numbers of chromosomes leads to cell death and tumor suppression.

[102]

**TÍTULO / TITLE:** - Altered Microenvironment Promotes Progression of Pre-Invasive Breast Cancer: myoepithelial expression of alpha6beta6 integrin in DCIS identifies high-risk patients and predicts recurrence.

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

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

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1504](https://doi.org/10.1158/1078-0432.CCR-13-1504)

**AUTORES / AUTHORS:** - Allen MD; Thomas GJ; Clark SE; Dawoud MM; Vallath S; Payne SJ; Gomm JJ; Dreger SA; Dickinson S; Edwards DR; Pennington CJ; Sestak I; Cuzick J; Marshall JF; Hart IR; Jones JL

**INSTITUCIÓN / INSTITUTION:** - Barts Cancer Institute, Queen Mary University of London, Barts and The London School of Medicine.

**RESUMEN / SUMMARY:** - PURPOSE: This study investigated the functional and clinical significance of integrin alpha6beta6 up-regulation in myoepithelial cells of ductal carcinoma in-situ (DCIS). EXPERIMENTAL DESIGN: Archival samples of DCIS and DCIS with associated invasion (n=532) were analysed for expression of alpha6beta6 by immunohistochemistry, and ability to predict recurrence and progression assessed in an independent, unique cohort of DCIS cases with long term follow up. Primary myoepithelial cells and myoepithelial cell lines, with and without alpha6beta6

expression, were used to measure the effect of alphavbeta6 on growth and invasion of tumor cell lines in vitro, and in a xenograft mouse model. Involvement of TGFbeta signaling was established using MLEC assay and antibody inhibition, and expression and activation of matrix-metalloproteinase (MMP)-9 established by RT-PCR and zymography. RESULTS: Expression of alphavbeta6 is significantly associated with progression to invasive cancer ( $p < 0.006$ ) and with recurrence over a median follow-up of 114 months in a series of matched DCIS cases treated with local excision. We show that expression of alphavbeta6 drives myoepithelial cells to promote tumor cell invasion in vitro and enhances mammary tumor growth in vivo. The tumor promoting effect of alphavbeta6-positive myoepithelial cells is dependent on TGFbeta-driven up-regulation of MMP9, and can be abrogated by inhibiting this pathway. CONCLUSION: These findings indicate that altered myoepithelial cells in DCIS predict disease progression and recurrence, and demonstrate that up-regulation of alphavbeta6 on myoepithelial cells generates a tumor-promoter function through TGFbeta up-regulation of MMP-9. These data suggest expression of alphavbeta6 may be used to stratify patients with DCIS.

[103]

**TÍTULO / TITLE:** - Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 1;31(31):3971-9. doi: 10.1200/JCO.2013.50.4910. Epub 2013 Oct 7.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2013.50.4910](#)

**AUTORES / AUTHORS:** - Morris PG; Correa DD; Yahalom J; Raizer JJ; Schiff D; Grant B; Grimm S; Lai RK; Reiner AS; Panageas K; Karimi S; Curry R; Shah G; Abrey LE; Deangelis LM; Omuro A

**INSTITUCIÓN / INSTITUTION:** - Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Anne S. Reiner, Kathy Panageas, Sasan Karimi, Richard Curry, Gaurav Shah, Lauren E. Abrey, Lisa M. DeAngelis, and Antonio Omuro, Memorial Sloan-Kettering Cancer Center; Rose K. Lai, Columbia University, New York, NY; Jeffrey J. Raizer and Sean Grimm, Northwestern University, Chicago, IL; David Schiff, University of Virginia, Charlottesville, VA; and Barbara Grant, University of Vermont, Burlington, VT.

**RESUMEN / SUMMARY:** - PURPOSE: A multicenter phase II study was conducted to assess the efficacy of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by consolidation reduced-dose whole-brain radiotherapy (rdWBRT) and cytarabine in primary CNS lymphoma. PATIENTS AND METHODS: Patients received induction chemotherapy with R-MPV (five to seven cycles); those achieving a complete response (CR) received rdWBRT (23.4 Gy), and otherwise, standard WBRT was offered (45 Gy). Consolidation cytarabine was given after the radiotherapy. The primary end point was 2-year progression-free survival (PFS) in patients receiving rdWBRT. Exploratory end points included prospective neuropsychological evaluation, analysis of magnetic resonance imaging (MRI) white matter changes using the Fazekas scale, and evaluation of the apparent diffusion coefficient (ADC) as a prognostic factor.

RESULTS: Fifty-two patients were enrolled, with median age of 60 years (range, 30 to 79 years) and median Karnofsky performance score of 70 (range, 50 to 100). Thirty-

one patients (60%) achieved a CR after R-MPV and received rdWBRT. The 2-year PFS for this group was 77%; median PFS was 7.7 years. Median overall survival (OS) was not reached (median follow-up for survivors, 5.9 years); 3-year OS was 87%. The overall (N = 52) median PFS was 3.3 years, and median OS was 6.6 years. Cognitive assessment showed improvement in executive function (P < .01) and verbal memory (P < .05) after chemotherapy, and follow-up scores remained relatively stable across the various domains (n = 12). All examined MRIs (n = 28) displayed a Fazekas score of  $\leq 3$ , and no patient developed scores of 4 to 5; differences in ADC values did not predict response (P = .15), PFS (P = .27), or OS (P = .33). CONCLUSION: R-MPV combined with consolidation rdWBRT and cytarabine is associated with high response rates, long-term disease control, and minimal neurotoxicity.

[104]

**TÍTULO / TITLE:** - Preclinical therapeutic efficacy of a novel pharmacological inducer of apoptosis in malignant peripheral nerve sheath tumors.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Nov 27.

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

[1934](#)

**AUTORES / AUTHORS:** - Chau V; Lim SK; Mo W; Liu C; Patel AJ; McKay RM; Wei S; Posner BA; De Brabander JK; Williams NS; Parada LF; Le LQ

**INSTITUCIÓN / INSTITUTION:** - Dermatology, UT Southwestern Medical Center.

**RESUMEN / SUMMARY:** - Neurofibromatosis Type 1 (NF1) is an autosomal disorder that affects neural crest-derived tissues, leading to a wide spectrum of clinical presentations. Patients commonly present with plexiform neurofibromas, benign but debilitating growths that can transform into malignant peripheral nerve sheath tumors (MPNSTs), a main cause of mortality. Currently, surgery is the primary course of treatment for MPNST, but with the limitation that these tumors are highly invasive. Radiation therapy is another treatment option, but is undesirable because it can induce additional mutations. MPNST patients may also receive doxorubicin as therapy, but this DNA-intercalating agent has relatively low tumor specificity and limited efficacy. In this study, we exploited a robust genetically-engineered mouse model of MPNST that recapitulates human NF1 associated MPNST to identify a novel small chemical compound that inhibits tumor cell growth. Compound 21 (Cpd21) inhibits growth of all available in vitro models of MPNST and human MPNST cell lines, while remaining non-toxic to normally-dividing Schwann cells or mouse embryonic fibroblasts. We show that this compound delays the cell cycle and leads to cellular apoptosis. Moreover, Cpd21 can reduce MPNST burden in a mouse allograft model, underscoring the compound's potential as a novel chemotherapeutic agent.

[105]

**TÍTULO / TITLE:** - The early discontinuation of adjuvant hormone therapy is associated with a poor prognosis in Japanese breast cancer patients.

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

**REVISTA / JOURNAL:** - Surg Today. 2013 Oct 19.

●● Enlace al texto completo (gratis o de pago) [1007/s00595-013-0762-7](#)

**AUTORES / AUTHORS:** - Taketani K; Tokunaga E; Yamashita N; Tanaka K; Akiyoshi S; Okada S; Ando K; Kimura Y; Saeki H; Oki E; Morita M; Kusumoto T; Maehara Y

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**RESUMEN / SUMMARY:** - **PURPOSE:** It is important for patients to complete the planned hormone therapy to reduce both the recurrence and mortality rates of hormone receptor-positive breast cancer. We investigated the rates and factors related to the early discontinuation of adjuvant hormone therapy at our institution. **METHODS:** We identified 145 females prescribed adjuvant hormone therapy who were followed up for longer than 5 years. The rate of completing the planned hormone therapy and factors related to early discontinuation were examined. The relapse-free survival rate was examined between the completion group and the discontinuation group.

**RESULTS:** The completion rate was 90.6 %. The primary reason for discontinuing hormone therapy within 5 years was side effects, such as arthritic pain. The primary factor related to early discontinuation was a significantly younger age. The relapse-free survival rate was significantly lower in the discontinuation group ( $p = 0.025$ ).

**CONCLUSIONS:** More than 90 % of the patients completed the planned adjuvant hormone therapy, and early discontinuation was related to a shorter RFS. To improve the rate of the successful completion of adjuvant hormone therapy, it is important to provide supportive care to reduce the occurrence of side effects and to care for young females with a desire to become pregnant.

[106]

**TÍTULO / TITLE:** - Clinical, genomic and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120).

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

**REVISTA / JOURNAL:** - Blood. 2013 Nov 6.

●● [Enlace al texto completo \(gratis o de pago\) 1182/blood-2013-07-515239](#)

**AUTORES / AUTHORS:** - Dhodapkar MV; Sexton R; Waheed S; Usmani S; Papanikolaou X; Nair B; Petty N; Shaughnessy JD Jr; Hoering A; Crowley J; Orlowski RZ; Barlogie B

**INSTITUCIÓN / INSTITUTION:** - Yale Cancer Center, Yale University, New Haven, CT, United States;

**RESUMEN / SUMMARY:** - All cases of clinical myeloma (CMM) are preceded by an asymptomatic monoclonal gammopathy (AMG), classified as either monoclonal gammopathy of undetermined significance (MGUS) or asymptomatic multiple myeloma (AMM). We analyzed data from AMG patients ( $n=331$ ) enrolled in a prospective observational clinical trial (S0120). Baseline data from clinical variables, gene expression profiles (GEP) of purified tumor cells, and findings of magnetic resonance imaging (MRI) were correlated with the risk of progression to CMM requiring therapy. GEP of purified tumor cells revealed that all molecular subtypes of CMM are also represented in the AMG phase. An increased risk score ( $>-0.26$ ) (based on a 70-gene signature, GEP70) was an independent predictor of the risk of progression to CMM. Combination of elevated serum free light chain, M-spike and GEP70 risk score identified a subset with high risk (67% at 2 years) of progression to CMM requiring therapy. Importantly, absence of these factors in AMM patients predicted low-risk

similar to MGUS. Detection of multiple (>1) focal lesions by MRI also conferred an increased risk of progression. These data demonstrate that signatures associated with high-risk CMM impact disease risk and support inclusion of genomic analysis in the clinical management of AMGs. This study is registered at ClinicalTrials.gov, identifier: NCT00900263.

[107]

**TÍTULO / TITLE:** - Adjuvant tamoxifen-induced mammographic breast density reduction as a predictor for recurrence in estrogen receptor-positive premenopausal breast cancer patients.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov 14.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10549-013-2726-4](#)

**AUTORES / AUTHORS:** - Ko KL; Shin IS; You JY; Jung SY; Ro J; Lee ES

**INSTITUCIÓN / INSTITUTION:** - Center for Breast Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 410-769, Republic of Korea.

**RESUMEN / SUMMARY:** - Tamoxifen is known to reduce the risk of breast cancer in women at high risk and also reduces mammographic breast density (MD) in a preventive setting. We investigated the efficacy of MD reduction (MDR) for predicting recurrence in estrogen receptor (ER)-positive patients in an adjuvant setting. A total of 1,066 ER-positive breast cancer patients who were enrolled in this study underwent curative surgery and received adjuvant tamoxifen for at least 2 years at our institution between January 2003 and December 2008. Using a computerized system, a single radiologist reviewed all mammograms and classified MD patterns on the basis of the Breast Imaging Reporting and Data System. MDR was assessed using the baseline mammogram taken before surgery (preMD) and the follow-up mammogram taken after the start of adjuvant tamoxifen (postMD). MDR positivity was defined as downgrading of the postMD grade, with the preMD grade as a reference. Patients were divided into 2 groups, MDR-positive and MDR-negative, for statistical analysis. Patients who showed MDR after an average of 19 months of adjuvant tamoxifen treatment had a 65 % lower risk of recurrence than patients who did not show MDR. Furthermore, significant risk reduction according to MDR had a predictive power for any type of recurrence pattern including loco-regional recurrence (87 % reduction) and systemic recurrence (52 % reduction) in ER-positive breast cancer patients, especially in women  $\leq 50$  years. In our study, only 4 patients (0.4 %) showed contralateral breast recurrence during the mean 61-month follow-up period and none of them experienced MDR. In conclusion, MDR during adjuvant tamoxifen therapy was independently associated with a lower risk of systemic and loco-regional recurrence in ER-positive breast cancer patients, especially in young women. For patients who do not experience MDR after approximately 1.5 years of tamoxifen therapy, more caution should be taken and other treatment strategies are warranted.

[108]

**TÍTULO / TITLE:** - Esterase D and gamma 1 actin level might predict results of induction therapy in patients with acute myeloid leukemia without and with maturation.

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

**REVISTA / JOURNAL:** - Med Oncol. 2013 Dec;30(4):725. doi: 10.1007/s12032-013-0725-2. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0725-2](https://doi.org/10.1007/s12032-013-0725-2)

**AUTORES / AUTHORS:** - Kazmierczak M; Luczak M; Lewandowski K; Handschuh L; Czyz A; Jarmuz M; Gniot M; Michalak M; Figlerowicz M; Komarnicki M

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**RESUMEN / SUMMARY:** - Development of modern proteomic methods in recent years has opened also new perspectives in the identification of new biomarkers which ensure more effective diagnosis, treatment monitoring and prediction of therapeutic outcome. We evaluated usefulness of comparative proteomics (MALDI-TOF) in two subtypes of acute myeloid leukemia (AML), M1 and M2, according to FAB classification. The bone marrow or blood cell proteomes were examined in 33 newly diagnosed patients before "3 + 7" induction therapy, after treatment and when the disease relapsed. We found that bone marrow and peripheral mononuclear cells from healthy volunteers revealed a number of quantitative and qualitative differences between the two proteomes, reflecting differences in the maturational status of normal cells. Such differences were not detected in our AML M1/M2 patients. Additionally, we found 9 proteins, which are potential biomarkers differentiating between the AML patients and healthy volunteers. Using comparative proteomics, we found that annexin I, glutathione transferase omega, esterase D and gamma 1 actin had prognostic significance. Applying statistical methods, we detected two proteins which might allow to predict results of induction therapy in AML M1/M2. One of them was esterase D, the higher concentration of which was associated with higher complete remission rate, and the other was gamma 1 actin, the higher concentration of which was related to resistance. In the article, we also discussed the role of these two proteins in the biology of AML, and we suggested potential usefulness of modification in induction therapy reflecting the presence of proteins.

[109]

**TÍTULO / TITLE:** - Anticipating the Clinical Use of Prognostic Gene Expression-Based Tests for Colon Cancer Stage II and III: Is Godot Finally Arriving?

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

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

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1769](https://doi.org/10.1158/1078-0432.CCR-13-1769)

**AUTORES / AUTHORS:** - Sveen A; Nesbakken A; Agesen TH; Guren MG; Tveit KM; Skotheim RI; Lothe RA

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Cancer Prevention, Institute for Cancer Research, The Norwegian Radium Hospital; Departments of Gastrointestinal Surgery and Oncology, Oslo University Hospital; and Centre for Cancer Biomedicine, Faculty of Medicine, University of Oslo, Oslo, Norway.

**RESUMEN / SUMMARY:** - PURPOSE: According to current recommendations for adjuvant treatment, patients with colon cancer stage II are not routinely offered chemotherapy, unless considered to have a high risk of relapse based on specific clinicopathological parameters. Following these criteria, it is challenging to identify the

subgroup of patients that will benefit the most from adjuvant treatment. Contrarily, patients with colon cancer stage III are routinely offered chemotherapy, but due to expected adverse effects and frailty, elderly patients are often excluded from standard protocols. Colon cancer is a disease of the elderly and accordingly, there is a large subgroup of patients for which guidelines for adjuvant treatment remain less clear. In these two clinical settings, improved risk stratification has great potential impact on patient care, anticipating that high-risk patients will benefit from chemotherapy. However, microsatellite instability is the only molecular prognostic marker recommended for clinical use. EXPERIMENTAL DESIGN: In this perspective, we provide an updated view on the status and clinical potential of the many proposed prognostic gene expression-based tests for colon cancer stage II and III. RESULTS: The main limitation for clinical implementation is lack of prospective validation. For patients with stage II, highly promising tests have been identified and clinical trials are ongoing. For elderly patients with stage III, the value of such tests has received less focus, but promising early results have been shown. CONCLUSION: Although awaiting results from prospective trials, improved risk assessment for patients with stage II and III is likely to be achieved in the foreseeable future. Clin Cancer Res; 1-9. ©2013 AACR.

[110]

**TÍTULO / TITLE:** - miR-34 is associated with poor prognosis of patients with gallbladder cancer through regulating telomere length in tumor stem cells.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Sep 28.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1207-z](#)

**AUTORES / AUTHORS:** - Jin K; Xiang Y; Tang J; Wu G; Li J; Xiao H; Li C; Chen Y; Zhao J

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology, Hunan Children's Hospital, Changsha, Hunan, 410007, China.

**RESUMEN / SUMMARY:** - miR-34a has been identified as a tumor suppressor in several tumors, but its involvement in gallbladder cancer (GBC) has not been reported. In this study, the miR-34a level and telomere length were measured in 77 gallbladder adenocarcinomas and 36 peritumoral tissues by real-time PCR. Forced miR-34a expression was established by an adenovirus carrying a miR-34a expression cassette. The colony-forming ability of isolated CD44+CD133+ GBC tumor stem-like cells was measured by matrigel colony assay. The xenograft tumor models were established by inoculating nude mice with CD44+CD133+ cells. Results showed that significantly lower miR-34a expression and longer telomere length were observed in gallbladder adenocarcinoma tissues, which correlated with poor prognosis of GBC patients. Forced overexpression of miR-34a inhibited the colony-forming ability of CD44+CD133+ GBC tumor stem-like cells in vitro and xenograft tumor growth in vivo. Injection of Ad-miR-34a downregulated PNUMS expression and reduced telomere length in xenograft GBC tumor cells. In conclusion, miR-34a is a tumor suppressor in gallbladder cancer. Both low miR-34a expression and long telomere length are markers for poor prognosis of patients with gallbladder adenocarcinoma. Our study also suggests that the miR-34a gene could be a target for targeting therapy of GBC.

[111]

**TÍTULO / TITLE:** - Differential expression and prognostic role of selected genes in colorectal cancer patients.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):4855-65.

**AUTORES / AUTHORS:** - Pitule P; Vycital O; Bruha J; Novak P; Hosek P; Treska V; Hlavata I; Soucek P; Kralickova M; Liska V

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**RESUMEN / SUMMARY:** - Aim: Colorectal cancer (CRC) is one of the most common malignant diseases. The aim of our study was to describe the expression status of 12 selected candidate genes, by comparing paired samples of healthy colon mucosa and tumour tissues and to correlate obtained data with clinical and pathological features, with the goal of revealing associations for individual gene expressions and tumour behaviour. MATERIALS AND METHODS: Samples from 53 patients with CRC were analyzed. Patients were divided into two groups based on the presence or absence of distant metastases at the time of primary tumour surgery. Expression levels were assessed by quantitative real-time polymerase chain reaction. RESULTS: We found changes in the expression of 10 out of 12 analyzed genes. Four genes were significantly up-regulated in tumour tissues: leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5;  $p < 0.001$ ), collagen triple helix repeat containing 1 (CTHRC1;  $p < 0.001$ ), visinin-like 1 (VSNL1;  $p < 0.001$ ) and versican (VCAN;  $p = 0.001$ ). Six genes were down-regulated: destrin (DSTN;  $p = 0.004$ ), mesoderm induction early response 1, family member 3 (MIER3;  $p < 0.001$ ), acyl-CoA synthetase long-chain family member 5 (ACSL5;  $p = 0.002$ ), mitogen-activated protein kinase 1/ERK (MAPK1;  $p < 0.001$ ), claudin 23 (CLDN23;  $p < 0.001$ ) and solute carrier family 26 (sulfate transporter), member 2 (SLC26A2;  $p < 0.001$ ). We recorded longer overall survival (OS) in the group of patients with higher expression of VSNL1 ( $p = 0.032$ ). Patients with more pronounced down-regulation of CLDN23 had shorter OS ( $p = 0.045$ ). In the group of patients without distant metastases, longer OS and disease-free interval (DFI) were found for patients with higher SLC26A2 expression in tumour tissues ( $p = 0.036$  and  $p = 0.011$ , respectively). In the same group, lower expression of VSNL1 in healthy tissue corresponded to a longer DFI ( $p = 0.020$ ), smaller decrease of SLC26A2 and ACSL5 meant longer DFI ( $p = 0.041$  and  $p = 0.040$ , respectively), as did greater increase of LGR5 expression ( $p = 0.026$ ). CONCLUSION: We identified differences in the expression of 10 genes in colorectal cancer tissue compared to healthy colon mucosa, and found prognostic significance for these changes which could be used for the development of a disease risk scoring system.

[112]

**TÍTULO / TITLE:** - Genetic variation in the GSTM3 promoter confer risk and prognosis of renal cell carcinoma by reducing gene expression.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 24. doi: 10.1038/bjc.2013.669.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.669](#)

**AUTORES / AUTHORS:** - Tan X; Wang Y; Han Y; Chang W; Su T; Hou J; Xu D; Yu Y; Ma W; Thompson TC; Cao G

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology, Second Military Medical University, 800 Xiangyin Road, Shanghai 200433, China.

**RESUMEN / SUMMARY:** - Background:Glutathione S-transferase mu 3 (GSTM3) has been proven to be downregulated in renal cell carcinoma (RCC). We aimed to characterise the role of GSTM3 and its genetic predisposition on the occurrence and postoperative prognosis of RCC.Methods:The effect of GSTM3 on RCC aggressiveness was examined using transfection and silencing methods. Glutathione S-transferase mu 3 expression in renal tissues was examined by immunohistochemistry. The associations of rs1332018 (A-63C) and rs7483 (V224I) polymorphisms with RCC risk were examined using 400 RCC patients and 802 healthy controls. The factors contributing to postoperative disease-specific survival of RCC patients were evaluated using the Cox proportional hazard model.Results:Glutathione S-transferase mu 3 silencing increased the invasion and anchorage-independent growth of RCC cell lines. rs1332018 (AC+CC vs AA), which correlated with low expression of GSTM3 in kidney, was associated with RCC risk (odds ratio, 1.446; 95% confidence interval (CI), 1.111-1.882). rs1332018 variants and low GSTM3 expression significantly predicted unfavourable postoperative survivals of RCC patients (P<0.05). rs1332018 variants independently predicted a poor prognosis (hazard ratio, 2.119; 95% CI, 1.043-4.307).Conclusion:Glutathione S-transferase mu 3 may function as a tumour suppressor in RCC. rs1332018 genetic variants predispose the host to downregulating GSTM3 expression in kidney, facilitate carcinogenesis, and predict an unfavourable postoperative prognosis of RCC.British Journal of Cancer advance online publication, 24 October 2013; doi:10.1038/bjc.2013.669 [www.bjcancer.com](http://www.bjcancer.com).

[113]

**TÍTULO / TITLE:** - Upstream mitogen-activated protein kinase (MAPK) pathway inhibition: MEK inhibitor followed by a BRAF inhibitor in advanced melanoma patients.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Oct 29. pii: S0959-8049(13)00876-9. doi: 10.1016/j.ejca.2013.09.014.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.09.014](http://1016/j.ejca.2013.09.014)

**AUTORES / AUTHORS:** - Goldinger SM; Zimmer L; Schulz C; Ugurel S; Hoeller C; Kaehler KC; Schadendorf D; Hassel JC; Becker J; Hauschild A; Dummer R

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**RESUMEN / SUMMARY:** - BRAF-mutant melanoma can be successfully treated by BRAF kinase inhibitors (BRAFi) and MEK kinase inhibitors (MEKi). However, the administration of BRAFi followed by MEKi did not generate promising response rate (RR). The purpose of this investigation was to evaluate the time to progression (TTP) with a mitogen-activated protein kinase (MAPK) pathway upstream inhibition strategy in BRAF mutated melanoma patients. BRAF mutation positive metastatic melanoma patients were identified within the Dermatology Cooperative Oncology Group (DeCOG) network and were treated first with a MEKi and upon progression with a selective BRAFi. A total of 23 melanoma patients (six females, 17 males, aged 47-80years) were

retrospectively analysed for TTP. The total median TTP was 8.9months. The median TTP for MEKi was 4.8 (1.2-23.2) and subsequent for BRAFi 4.5 (1.2-15.7) months, respectively. A higher RR for MEKi (39%, nine partial responses and 0 complete responses) than previously reported was observed. Our analysis suggests that the reversed inhibition of the MAPK pathway is feasible in BRAF mutated melanoma. The median TTP (8.9months) is close to the promising BRAF- and MEKi combination therapy (median progression-free survival (PFS) 9.4months). The total treatment duration of the MAPK inhibition when a MEKi is administered first is similar compared to the reversed sequence, but TTP shifts in favour to the MEKi. This approach is feasible with reasonable tolerability. This clinical investigation encourages further studies in prospective clinical trials to define the optimal treatment schedule for the MAPK pathway inhibition and should be accompanied by molecular monitoring using repeated biopsies.

[114]

**TÍTULO / TITLE:** - Indomethacin Sensitizes TRAIL-Resistant Melanoma cells to TRAIL-induced Apoptosis through ROS-mediated Up-regulation of Death Receptor 5 and Down-regulation of Survivin.

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

**REVISTA / JOURNAL:** - J Invest Dermatol. 2013 Nov 8. doi: 10.1038/jid.2013.471.

●● Enlace al texto completo (gratis o de pago) [1038/jid.2013.471](#)

**AUTORES / AUTHORS:** - Tse AW; Cao HH; Cheng CY; Kwan HY; Yu H; Fong WF; Yu ZL

**INSTITUCIÓN / INSTITUTION:** - Centre for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, China.

**RESUMEN / SUMMARY:** - TRAIL has attracted considerable attention owing to its selective killing of tumor cells but not normal cells. Melanoma shows weak response to TRAIL because of its low level of TRAIL death receptors. Here, we investigated whether indomethacin, a non-steroidal anti-inflammatory drug, can potentiate TRAIL-induced apoptosis in melanoma cells. We showed that indomethacin was capable of promoting TRAIL-induced cell death and apoptosis in A375 melanoma cells. Mechanistically, indomethacin induced cell surface expression of death receptor 5 (DR5) in melanoma cells and also in various types of cancer cells. DR5 knockdown abolished the enhancing effect of indomethacin on TRAIL responses. Induction of the DR5 by indomethacin was found to be p53-independent but dependent on the induction of CHOP. Knockdown of CHOP abolished indomethacin-induced DR5 expression and the associated potentiation of TRAIL-mediated cell death. In addition, indomethacin-induced ROS production preceded up-regulation of CHOP and DR5, and consequent sensitization of cells to TRAIL. We also found that indomethacin treatment down-regulated survivin via ROS as well as the NF-kappaB-mediated signaling pathways. Interestingly, indomethacin also converted TRAIL-resistant melanoma MeWo and SK-MEL-5 cells into TRAIL-sensitive cells. Taken together, our results indicate that indomethacin can potentiate TRAIL-induced apoptosis through up-regulation of death receptors and down-regulation of survivin. Journal of Investigative Dermatology accepted article preview online, 8 November 2013; doi:10.1038/jid.2013.471.

[115]

**TÍTULO / TITLE:** - Prognostic and Predictive Blood-Based Biomarkers in Patients with Advanced Pancreatic Cancer: Results from CALGB80303 (Alliance).

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 12.

- Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0926](#)

**AUTORES / AUTHORS:** - Nixon AB; Pang H; Starr MD; Friedman PN; Bertagnolli MM; Kindler HL; Goldberg RM; Venook AP; Hurwitz HI

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Division of Medical Oncology; Alliance Statistics and Data Center, Duke University Medical Center; Durham, North Carolina; Section of Hematology/Oncology, University of Chicago Cancer Research Center; Chicago, Illinois; Department of Surgery, Brigham and Women's Hospital & Harvard Medical School; Boston, Massachusetts; Department of Internal Medicine, Ohio State University; Columbus, Ohio; and Division of Medical Oncology, University of California, San Francisco, California.

**RESUMEN / SUMMARY:** - PURPOSE: CALGB80303 was a phase III trial of 602 patients with locally advanced or metastatic pancreatic cancer comparing gemcitabine/bevacizumab versus gemcitabine/placebo. The study found no benefit in any outcome from the addition of bevacizumab to gemcitabine. Blood samples were collected and multiple angiogenic factors were evaluated and then correlated with clinical outcome in general (prognostic markers) and with benefit specifically from bevacizumab treatment (predictive markers). EXPERIMENTAL DESIGN: Plasma samples were analyzed via a novel multiplex ELISA platform for 31 factors related to tumor growth, angiogenesis, and inflammation. Baseline values for these factors were correlated with overall survival (OS) using univariate Cox proportional hazard regression models and multivariable Cox regression models with leave-one-out cross validation. Predictive markers were identified using a treatment by marker interaction term in the Cox model. RESULTS: Baseline plasma was available from 328 patients. Univariate prognostic markers for OS were identified including: Ang2, CRP, ICAM-1, IGFBP-1, TSP-2 (all  $P < 0.001$ ). These prognostic factors were found to be highly significant, even after adjustment for known clinical factors. Additional modeling approaches yielded prognostic signatures from multivariable Cox regression. The gemcitabine/bevacizumab signature consisted of IGFBP-1, interleukin-6, PDGF-AA, PDGF-BB, TSP-2; whereas the gemcitabine/placebo signature consisted of CRP, IGFBP-1, PAI-1, PDGF-AA, P-selectin (both  $P < 0.0001$ ). Finally, three potential predictive markers of bevacizumab efficacy were identified: VEGF-D ( $P < 0.01$ ), SDF1 ( $P < 0.05$ ), and Ang2 ( $P < 0.05$ ). CONCLUSION: This study identified strong prognostic markers for pancreatic cancer patients. Predictive marker analysis indicated that plasma levels of VEGF-D, Ang2, and SDF1 significantly predicted for benefit or lack of benefit from bevacizumab in this population. Clin Cancer Res; 1-10. ©2013 AACR.

[116]

**TÍTULO / TITLE:** - Changes of cytokines in patients with liver cirrhosis and advanced hepatocellular carcinoma treated by sorafenib.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2344-1](http://1007/s00280-013-2344-1)

**AUTORES / AUTHORS:** - Nagai H; Kanekawa T; Kobayashi K; Mukozu T; Matsui D; Matsui T; Kanayama M; Wakui N; Momiyama K; Shinohara M; Ishii K; Igarashi Y; Sumino Y

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology and Hepatology, Department of Internal Medicine (Omori), Faculty of Medicine, School of Medicine, Toho University, 6-11-1, Omorinishi, Ota-ku, Tokyo, 143-8541, Japan, [hidinari@aol.com](mailto:hidinari@aol.com).

**RESUMEN / SUMMARY:** - PURPOSE: Recently, the oral multikinase inhibitor sorafenib has been used to treat advanced hepatocellular carcinoma (aHCC). Tumor necrosis factor (TNF) induces apoptosis of tumor cells by binding to TNF-related apoptosis-inducing ligand, while binding of the Fas ligand on cytotoxic T lymphocytes to the Fas receptor on hepatocytes also causes apoptosis. The aim of this study was to retrospectively evaluate changes of cytokines in patients with liver cirrhosis (LC) and aHCC receiving sorafenib therapy. METHODS: Fifty-seven adult Japanese LC patients received sorafenib for aHCC (200-800 mg/day for 4 weeks) between 2009 and 2012 at our hospital. Blood samples were collected in the early morning before and after treatment, and the serum levels of soluble TNF-alpha (sTNF-alpha), soluble TNF receptor (sTNF-R), soluble Fas ligand (sFas L), and soluble Fas (sFas) were evaluated. RESULTS: Ten patients were treated with sorafenib at 200 mg/day (200 mg group), 37 patients were given 400 mg/day (400 mg group), and 10 patients received 800 mg/day (800 mg group). The serum level of sTNF-alpha was significantly increased after treatment compared with before treatment in the 400 and 800 mg groups. The serum level of sTNF-R also showed a significant increase after treatment in the 400 mg group, although there was no significant difference of sTNF-R between before and after treatment in the 200 and 800 mg groups. sFas showed a significant decrease after treatment compared with before treatment in the 400 and 800 mg groups, although the serum level of sFas L never exceeded 0.15 ng/ml. CONCLUSIONS: These findings suggest that treatment with sorafenib at doses  $\geq$ 400 mg/day might promote TNF-related or Fas-related apoptosis by increasing the circulating level of TNF-alpha or decreasing that of sFas.

[117]

**TÍTULO / TITLE:** - Anterior Gradient 2 and Mucin 4 Expression Mirrors Tumor Cell Differentiation in Pancreatic Adenocarcinomas, But Aberrant Anterior Gradient 2 Expression Predicts Worse Patient Outcome in Poorly Differentiated Tumors.

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

**REVISTA / JOURNAL:** - Pancreas. 2013 Oct 30.

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

[1097/MPA.0b013e3182a63bc3](http://1097/MPA.0b013e3182a63bc3)

**AUTORES / AUTHORS:** - Brychtova V; Hermanova M; Karasek P; Lenz J; Selingerova I; Vojtesek B; Kala Z; Hrstka R

**INSTITUCIÓN / INSTITUTION:** - From the \*Regional Centre for Applied Molecular Oncology, Masaryk Memorial Cancer Institute; daggerFirst Department of Pathological Anatomy, St Anne's University Hospital, Medical Faculty of Masaryk University; double daggerDepartment of Complex Oncology Care, Masaryk Memorial Cancer Institute;

Department of Mathematics and Statistics, Faculty of Science, Masaryk University; and parallel Department of Surgery, University Hospital Brno, Medical Faculty of Masaryk University, Brno, Czech Republic.

**RESUMEN / SUMMARY:** - OBJECTIVES: This study aimed to determine anterior gradient 2 (AGR2) expression in biopsies from pancreatic ductal adenocarcinomas (PDACs) and to evaluate AGR2 as a potential independent prognostic factor. METHODS: Tissue sample sections from a cohort of 135 consecutive surgically resectable PDACs were subjected to semiquantitative immunohistochemical analysis of AGR2 and mucin 4 (MUC4) expression. RESULTS: Anterior gradient 2 was over-expressed in PDAC compared with normal ductal cells. Since tumor lesions of PDAC are heterogeneous and constitute structures with various differentiation states, expression of both AGR2 and MUC4 was evaluated in each separate component. Expression levels of both proteins reflected the degree of tumor differentiation. Generally, well differentiated regions of tumor lesions expressed high levels of both proteins, moderately differentiated regions showed less AGR2 and MUC4, and poorly differentiated structures showed only weak positivity or were entirely negative. Of particular interest were occasional cases of strong AGR2 expression in high-grade tumors, where elevated protein levels were associated with shorter patient survival. CONCLUSIONS: Anterior gradient 2 and MUC4 reflect the level of differentiation of PDACs. However, in less differentiated tumors, aberrantly elevated AGR2 expression predicts poor patient outcome.

[118]

**TÍTULO / TITLE:** - High expression of nucleobindin 2 mRNA: an independent prognostic factor for overall survival of patients with prostate cancer.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1268-z](#)

**AUTORES / AUTHORS:** - Zhang H; Qi C; Wang A; Li L; Xu Y

**INSTITUCIÓN / INSTITUTION:** - National Key Clinical Specialty of Urology, Second Affiliated Hospital of Tianjin Medical University, Tianjin Key Institute of Urology, 23 Pingjiang Road, Hexi District, Tianjin, 300211, China.

**RESUMEN / SUMMARY:** - Nucleobindin 2 (NUCB2) has been demonstrated to play critical roles in tumorigenesis and tumor development of breast cancer. The expression change of nucleobindin 2 at mRNA level in prostate cancer (PCa) tissues compared with adjacent benign prostate tissues was detected by using real-time quantitative reverse transcriptase-polymerase chain reaction analysis in our previous study. The data suggests that NUCB2 is a cancer-related gene associated with the aggressive progression and biochemical recurrence-free survival predictor of PCa patients. However, the correlation between the expression of the NUCB2 mRNA and the overall survival of patients with PCa was not analyzed. Thus, the association of NUCB2 mRNA expression with overall survival of PCa patients was analyzed in this study. Kaplan-Meier analysis and Cox proportional hazards regression models were used to investigate the correlation between NUCB2 mRNA expression and prognosis of PCa patients. The Kaplan-Meier survival analysis showed that the high expression of NUCB2 was related to the poor overall survival of patients with PCa. Multivariate Cox analysis showed that NUCB2 mRNA was an independent prognostic factor for overall

survival of patients with PCa. In conclusion, we demonstrated that high NUCB2 mRNA expression correlated with poor overall survival in patients with PCa.

[119]

**TÍTULO / TITLE:** - The diarylheptanoid hirsutenone sensitizes chemoresistant ovarian cancer cells to cisplatin via modulation of Apoptosis Inducing Factor and X-linked Inhibitor of Apoptosis.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 18.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.513879](#)

**AUTORES / AUTHORS:** - Farrand L; Kim JY; Byun S; Im-Aram A; Lee J; Suh JY; Lee KW; Lee HJ; Tsang BK

**INSTITUCIÓN / INSTITUTION:** - Seoul National University, Korea, Republic of;

**RESUMEN / SUMMARY:** - Cisplatin (CDDP) and its derivatives are considered first-line treatments for ovarian cancer (OVCA). However, despite initial results that often appear promising, in most cases patients will return with recurrent disease that fails to respond to further chemotherapy. We assayed a number of food phytochemicals with reported PI3K inhibitory ability to identify candidates that can influence CDDP treatment outcomes in chemoresistant OVCA cell lines. A direct comparison revealed that the diarylheptanoid hirsutenone from the tree bark of *Alnus hirsuta* var. *sibirica* was superior at inducing CDDP sensitivity in a number of chemoresistant cancer cell lines. While hirsutenone treatment activated p53, its modest efficacy in p53-mutant and null cell lines suggested the existence of a p53-independent mode of action. Further investigation revealed that hirsutenone causes CDDP-dependent apoptosis in chemoresistant cells by ubiquitin-proteasome-dependent XIAP degradation and by enhancing the translocation of AIF from the mitochondria to the nucleus. This was found to be, at least in part, under the influence of upstream Akt activity, linking hirsutenone-dependent PI3K inhibition with downstream effects on AIF, XIAP and apoptosis. Our findings provide rationale for further investigation of the effects of hirsutenone on chemoresistant OVCA in clinical studies.

[120]

**TÍTULO / TITLE:** - Correlation of IDH1/2 mutation with clinicopathologic factors and prognosis in anaplastic gliomas: a report of 203 patients from China.

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

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 Oct 23.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1519-9](#)

**AUTORES / AUTHORS:** - Zhang CB; Bao ZS; Wang HJ; Yan W; Liu YW; Li MY; Zhang W; Chen L; Jiang T

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100050, China.

**RESUMEN / SUMMARY:** - PURPOSE: Isocitrate dehydrogenase (IDH) gene mutation is one of the most exciting new advances in these years. It has been reported that IDH gene frequently altered in grade II and grade III gliomas. We aimed to identify the mutation frequency of IDH genes in Chinese anaplastic glioma patients, the association of IDH gene mutation with other clinical and molecular pathological features and the

prognostic value of it. METHODS: We performed polymerase chain reaction-based IDH gene mutation detection in 203 anaplastic glioma patients from China. RESULTS: A total of 108 and 3 patients harbored IDH1 and IDH2 gene mutation, respectively. And there was a higher proportion of MGMT promoter methylation, frontal lobe location, and better outcome and lower proportion of temporal location in IDH-mutated samples. There were hardly any significant association between protein expression level of well-known markers and IDH mutation. Anaplastic oligoastrocytoma and anaplastic astrocytoma patients with IDH gene mutation showed similar prognosis with anaplastic oligodendroglioma patients with wild-type IDH gene. CONCLUSIONS: IDH gene mutation is a good prognostic marker and a potential substratification factor for anaplastic glioma patients.

[121]

**TÍTULO / TITLE:** - Single cell imaging of the heat shock response during proteasome inhibitor-induced apoptosis in colon cancer cells suggests that magnitude and length rather than time of onset determines resistance to apoptosis.

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

**REVISTA / JOURNAL:** - J Cell Sci. 2013 Nov 27.

●● Enlace al texto completo (gratis o de pago) [1242/jcs.137158](#)

**AUTORES / AUTHORS:** - Ramapathiran L; Bernas T; Walter F; Williams L; Dussmann H; Concannon CG; Prehn JH

**RESUMEN / SUMMARY:** - Targeting the proteasome is a valuable approach for cancer therapy, potentially limited by pro-survival pathways induced in parallel to cell death. Whether these pro-survival pathways are activated in all cells, show different activation kinetics in sensitive versus resistant cells, or interact functionally with cell death pathways is unknown. We monitored activation of the heat shock response (HSR), a key survival pathway induced by proteasome inhibition, relative to apoptosis activation in HCT116 colon cancer cells expressing green fluorescent protein (GFP) under the control of the Hsp70 promoter. Single cell and high content time-lapse imaging of epoxomicin treatment revealed that neither basal activity, nor the time of onset of the HSR differed between resistant and sensitive populations. However, resistant cells had significantly higher and prolonged reporter activity than those that succumbed to cell death. p53 deficiency protected against cell death but failed to modulate the HSR. In contrast, inhibition of the HSR significantly increased the cytotoxicity of epoxomicin. Our data provide novel insights into the kinetics and heterogeneity of HSR during proteasome inhibition, suggesting that the HSR modulates cell death signaling unidirectionally.

[122]

**TÍTULO / TITLE:** - Evaluation of circulating Transforming growth factor-beta1, Glypican-3 and Golgi protein-73 mRNAs expression as predictive markers for hepatocellular carcinoma in Egyptian patients.

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

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 Dec;40(12):7069-75. doi: 10.1007/s11033-013-2829-3. Epub 2013 Nov 2.

●● Enlace al texto completo (gratis o de pago) [1007/s11033-013-2829-3](#)

**AUTORES / AUTHORS:** - Ibrahim GH; Mahmoud MA; Aly NM

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Biochemistry, Faculty of Medicine, Suez Canal University, Round Road, Ismailia, 41111, Egypt, [dr\\_ghamer@yahoo.fr](mailto:dr_ghamer@yahoo.fr).

**RESUMEN / SUMMARY:** - Hepatocellular carcinoma (HCC) incidence is fast-growing especially in countries highly prevalent with viral hepatitis. Its poor prognosis has driven the research toward the discovery of sensitive markers for early detection. We investigated the usefulness of serum Transforming growth factor-beta1 (TGF-beta1), Glypican-3 (GPC3), and Golgi protein-73 (GP73) mRNAs as early biomarkers in HCC Egyptian patients chronically infected with hepatitis C virus (HCV) in comparison with serum alpha-fetoprotein (AFP). Using semi-quantitative RT-PCR and densitometry analysis, circulating TGF-beta1, GPC3, and GP73 mRNAs expressions were estimated in 15 healthy adults, 15 chronic HCV (CHC) patients and 25 HCC patients. Serum GP73 expression percentage in HCC group was significantly higher than controls (100 vs. 40 %,  $P \leq 0.001$ ) and when compared to elevated serum AFP levels (100 vs. 36 %,  $P \leq 0.001$ ). TGF-beta1 and GP73 expression means were also higher in HCC patients than controls and CHC patients ( $P < 0.05$ ). GPC3 expression showed higher frequency in CHC patients compared to HCC group (80 vs. 28 %,  $P = 0.0016$ ). According to the study cutoffs, serum TGF-beta1 and GP73 mRNAs showed 60 and 96 % sensitivities for HCC diagnosis with 100 and 95 % specificities, respectively. Furthermore, elevated GP73 mRNA expression levels in early HCC were significantly increased compared to those of TGF-beta1 mRNA and to high serum AFP (92.3 vs. 53.8 and 23.1 %,  $P = 0.03$  and  $0.0004$ , respectively). In conclusion, circulating TGF-beta1 and GP73 mRNAs could be useful biomarkers for HCV-induced HCC diagnosis. Moreover, serum GP73 mRNA is sensitive for early cancer detection than AFP and TGF-beta1 mRNA. However, these results need further validation studies.

[123]

**TÍTULO / TITLE:** - Posttransplant next-generation or Sanger sequencing predicts clinical relapse in patients with myelodysplastic/myeloproliferative neoplasms.

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

**REVISTA / JOURNAL:** - Eur J Haematol. 2013 Oct 25. doi: 10.1111/ejh.12223.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ejh.12223](#)

**AUTORES / AUTHORS:** - Fu Y; Schroeder T; Zabelina T; Badbaran A; Bacher U; Kobbe G; Ayuk F; Wolschke C; Schnittger S; Kohlmann A; Haferlach T; Kroger N

**INSTITUCIÓN / INSTITUTION:** - Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

**RESUMEN / SUMMARY:** - Relapse is the major cause of treatment failure after allogeneic stem-cell transplantation (AH SCT) for patients with myelodysplastic syndrome/myeloproliferative syndrome neoplasms (MDS/MPN). We evaluated the impact of molecular mutations on outcome and the value of molecular monitoring post-transplantation. We screened 45 patients with chronic myelomonocytic leukemia (n = 39 patients, including seven with transformed-acute myeloid leukemia), MDS/MPN unclassifiable (n = 5), and atypical BCR-ABL1-negative CML (n = 1) for mutations in ASXL1, CBL, NRAS, and TET2 genes by molecular genetics including a sensitive next-generation sequencing (NGS) technique. In 36 patients, sufficient DNA was available

for molecular analyses. In particular, TET2 and CBL mutations were screened applying amplicon deep sequencing. In 89% of cases, at least one mutation could be detected: ASXL1: n = 18 (50%); CBL: n = 7 (19%); TET2: n = 15 (42%); and NRAS: n = 11 (32%). Survival after AHSCT at 5 yr was 46% (95% CI 28-64%) and was not influenced by any mutation. After a median of 6 months after AHSCT in 33% of the patients, one of the molecular markers was still detectable, resulting in a higher incidence of relapse than in patients with undetectable mutations (50% vs. 15%, P = 0.04). In conclusion, pretransplant molecular mutation analysis can help to detect biomarkers in patients with MPN/MDS, which may be subsequently used as minimal residual disease markers after AHSCT.

[124]

**TÍTULO / TITLE:** - Outcome of allotransplants in patients with chronic-phase chronic myeloid leukemia following imatinib failure: prognosis revisited.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4663-7.

**AUTORES / AUTHORS:** - Liu YC; Hsiao HH; Chang CS; Liu TC; Yang WC; Hsu JF; Huang CT; Cho SF; Wu CH; Tsai YF; Lin SF

**INSTITUCIÓN / INSTITUTION:** - 100, Tzyou 1<sup>st</sup> Road, Kaohsiung, 807, Taiwan, ROC. [shlin@kmu.edu.tw](mailto:shlin@kmu.edu.tw).

**RESUMEN / SUMMARY:** - BACKGROUND: The outcome of allotransplants in patients with chronic -phase (CP) chronic myeloid leukemia (CML) who progressed to accelerated phase (AP) or blast phase (BP) following imatinib failure, especially those without preceding suboptimal response, remains unclear. PATIENTS AND METHODS: One hundred and five patients with newly-diagnosed CML-CP were retrospectively reviewed. Sixty-six patients received first-line imatinib therapy, 26 received interferon followed by imatinib, and 13 received front-line allotransplants. RESULTS: No significant differences were found in overall survival ( $p=0.57$ ) and blast-free survival ( $p=0.25$ ) between different first-line therapies. Among 66 imatinib-treated patients, 18 (27.3%) developed imatinib failure, 14 (21.2%) progressed to AP/BP, including eight without preceding suboptimal response. Compared to front-line allotransplant, patients with imatinib failure had a significantly worse overall survival after allotransplants ( $p=0.015$ ), mainly due to an increase of treatment-related mortality. CONCLUSION: Early recognition of imatinib-treated patients who should receive an allotransplant is important rather than waiting until imatinib failure with disease progression.

[125]

**TÍTULO / TITLE:** - Prospective phase II study of rituximab with alternating cycles of hyper-CVAD and high-dose methotrexate with cytarabine for young patients with high-risk diffuse large B-cell lymphoma.

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

**REVISTA / JOURNAL:** - Br J Haematol. 2013 Dec;163(5):611-20. doi: 10.1111/bjh.12585. Epub 2013 Oct 1.

- Enlace al texto completo (gratis o de pago) [1111/bjh.12585](#)

**AUTORES / AUTHORS:** - Oki Y; Westin JR; Vega F; Chuang H; Fowler N; Neelapu S; Hagemeister FB; McLaughlin P; Kwak LW; Romaguera JE; Fanale M; Younes A; Rodriguez MA; Orlowski RZ; Wang M; Ouzounian ST; Samaniego F; Fayad L

**INSTITUCIÓN / INSTITUTION:** - Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

**RESUMEN / SUMMARY:** - We conducted a prospective randomized phase II study to evaluate two chemotherapy regimens: (i) rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (R-HCVAD) alternating with rituximab, high-dose methotrexate, and cytarabine (R-MA) and (ii) rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in diffuse large B-cell lymphoma (DLBCL). This study randomized patients aged  $\leq 60$  years with DLBCL and an age-adjusted international prognostic index  $\geq 2$  to R-HCVAD/R-MA or R-CHOP based on a Bayesian adaptive algorithm. Interim analysis of the first 26 eligible patients showed that the complete response rate (CRR) was higher with R-HCVAD/R-MA than R-CHOP ( $P = 0.03$ ); thus, R-CHOP arm was closed. In the final analysis, 49 and 10 eligible patients were treated in R-HCVAD/R-MA and R-CHOP arms respectively; CRR were 82% and 60% respectively ( $P = 0.13$ ); 3-year progression-free survival (PFS) rates were 75.7% and 77.8% respectively ( $P = 0.53$ ). In the R-HCVAD/R-MA arm, 3-year PFS rates in patients aged 46-60 years and  $\leq 45$  years were 70.3% and 87.1% respectively ( $P = 0.13$ ), and the treatment-associated early mortality rate in patients  $>45$  years was 12%. In conclusion, R-HCVAD/R-MA is associated with excellent outcome in patients  $\leq 45$  years old. However, in patients  $>45$  years old, R-HCVAD/R-MA is associated with unacceptable mortality rates.

[126]

**TÍTULO / TITLE:** - Rapid response of breast cancer to neoadjuvant intramammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer.

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

**REVISTA / JOURNAL:** - Menopause. 2013 Oct 21.

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

[1097/GME.0000000000000096](#)

**AUTORES / AUTHORS:** - Glaser RL; Dimitrakakis C

**INSTITUCIÓN / INSTITUTION:** - From the 1Millennium Wellness Center, Dayton, OH; 2Department of Surgery, Wright State University Boonshoft School of Medicine, Dayton, OH; 3First Department of Ob/Gyn, Athens University Medical School, Athens, Greece; and 4Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Experimental and clinical data support the inhibitory effect of testosterone on breast tissue and breast cancer. However, testosterone is aromatized to estradiol, which exerts the opposite effect. The aim of this study was to determine the effect of testosterone, combined with the aromatase inhibitor anastrozole, on a hormone receptor positive, infiltrating ductal carcinoma in the neoadjuvant setting. **METHODS:** To determine clinical response, we obtained serial ultrasonic measurements and mammograms before and after therapy. Three combination implants-each containing 60 mg of testosterone and 4 mg of anastrozole-were placed anterior, superior, and inferior to a 2.4-cm tumor in the left breast. Three additional testosterone-anastrozole implants were again placed peritumorally 48 days

later. RESULTS: By day 46, there was a sevenfold reduction in tumor volume, as measured on ultrasound. By week 13, we documented a 12-fold reduction in tumor volume, demonstrating a rapid logarithmic response to intramammary testosterone-anastrozole implant therapy, equating to a daily response rate of 2.78% and a tumor half-life of 23 days. Therapeutic systemic levels of testosterone were achieved without elevation of estradiol, further demonstrating the efficacy of anastrozole combined with testosterone. CONCLUSIONS: This novel therapy, delivered in the neoadjuvant setting, has the potential to identify early responders and to evaluate the effectiveness of therapy in vivo. This may prove to be a new approach to both local and systemic therapies for breast cancer in subgroups of patients. In addition, it can be used to reduce tumor volume, allowing for less surgical intervention and better cosmetic oncoplastic results. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

<http://creativecommons.org/licenses/by-nc-nd/3.0>.

[127]

**TÍTULO / TITLE:** - The prognostic significance of WNT pathway in surgically-treated colorectal cancer: beta-catenin expression predicts for disease-free survival.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4573-84.

**AUTORES / AUTHORS:** - Kamposioras K; Konstantara A; Kotoula V; Lakis S; Kouvatseas G; Akriviadis E; Vrettou E; Dionysopoulos D; Krikelis D; Papadopoulou K; Charalambous E; Chrisafi S; Konstantaras C; Fountzilias G

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, University Hospital of Larissa, 41 110 Larissa, Greece. [kambkons1@yahoo.gr](mailto:kambkons1@yahoo.gr).

**RESUMEN / SUMMARY:** - BACKGROUND: The wingless-type MMTV integration site family of proteins (WNT) pathway is highly involved in colorectal cancer development. The aim of this study was to explore the prognostic significance and clinicopathological correlations of this pathway in a cohort of surgically-treated patients with non-metastatic colorectal cancer in relation to the site of expression of pathway proteins. MATERIALS AND METHODS: Immunohistochemical expression of nuclear cyclin D1, membranous E-cadherin and P-cadherin, membranous and nuclear beta-catenin in the invasive front (IF), the tumor center (TC), as well as their mean, were assessed in 106 paraffin-embedded tissue samples. Adenomatous Polyposis Coli (APC), Axin-2 (AXIN2), cyclin-D1 (CCND1), Matrix Metalloproteinase-7 (MMP7), Secreted Frizzled Related Protein (SFRP) 1, 2 and 4 and WNT5A were evaluated by RT PCR. RESULTS: Membranous beta-catenin expression was statistically reduced in the IF. Cyclin-D1 was reduced in tumors arising closer to the rectum. Reduced nuclear expression of cyclin-D1 in the IF was associated with lymphatic, venous and perineural invasion. Loss of membranous beta-catenin in the TC was more common among N2 tumors. Higher SFRP4 mRNA was associated with advanced T stage. In univariate analysis, membranous expression of beta-catenin in TC and IF, and their mean, was associated with longer disease-free survival (DFS). In multivariate analysis, tumor stage and mean beta-catenin expression were prognostic for longer DFS (hazard ratio=0.33; p=0.01). beta-Catenin expression in the IF remained significant when the

mean expression was not included in the multivariate analysis (hazard ratio=0.41; p=0.028). CONCLUSION: Mean membranous expression of beta-catenin, as well as that in the IF, is prognostic for longer DFS in patients with non metastatic colorectal cancer.

[128]

**TÍTULO / TITLE:** - C-Reactive Protein Is a Negative Independent Factor in Patients with Stage IV Colorectal Cancer Undergoing Oxaliplatin-based Chemotherapy.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):5051-5.

**AUTORES / AUTHORS:** - Fukuchi M; Kuwabara K; Tsuji Y; Baba H; Ishibashi K; Chika N; Hatano S; Matsuzawa T; Kumamoto K; Kumagai Y; Mochiki E; Ishida H

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**RESUMEN / SUMMARY:** - Background/Aim: To determine the clinical significance of C-reactive protein (CRP) concentration in patients with stage IV colorectal cancer (CRC) undergoing oxaliplatin-based chemotherapy. PATIENTS AND METHODS: We retrospectively reviewed the medical charts of 112 patients with stage IV CRC who had received modified FOLFOX6 (5-fluorouracil, oxaliplatin, leucovorin) between January 2006, and December 2010 and used Cox's proportional hazard model to determine for independent prognostic factors of survival. We generated receiver operating characteristics (ROC) curves to determine the optimal cut-off for the discrimination of the duration of survival by CRP concentration. RESULTS: According to the multivariate analysis, increased CRP concentration (p=0.04) and non-curative surgery (p<0.01) were independent unfavorable factors for survival, and the optimal cut-off CRP concentration according to dichotomized duration of survival (3-24 months) ranged from 0.8 to 1.2 mg/dl. CONCLUSION: Pre-chemotherapy CRP concentrations may be useful for predicting survival of patients with stage IV CRC.

[129]

**TÍTULO / TITLE:** - Mitogen-activated protein kinases in gliomas and correlation with patients' prognosis.

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

**REVISTA / JOURNAL:** - Acta Neurol Scand. 2013 Sep 20. doi: 10.1111/ane.12175.

●● Enlace al texto completo (gratis o de pago) [1111/ane.12175](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Medical School, University Hospital of Patras, Patras, Greece.

**RESUMEN / SUMMARY:** - OBJECTIVE: We examined the activation of the mitogen-activated protein kinases (MAPKs) signaling pathway in a cohort of brain gliomas, by taking advantage of a series of phosphorylation state-specific antibodies against phospho-p44/42(ERK1/2), phospho-p38, and phospho-JNK. Potential correlations between expression profiles of phospho-p44/42(ERK1/2), phospho-p38, and phospho-JNK and tumor grade, age, gender, overall survival, and Ki-67 status were also

explored. METHODS: Immunohistochemistry was performed in formalin-fixed, paraffin-embedded tissues of 87 serial brain biopsies sequentially obtained for diagnostic purposes in a period of 9 years (2000-2008) from an equal number of patients with low- and high-grade gliomas. RESULTS: Higher expression of all proteins in high-grade gliomas was documented. The univariate analysis revealed that high phospho-p44/42(ERK1/2) and high phospho-JNK expressions were strongly associated with decreased overall survival. However, the multivariate Cox regression failed to consider those markers as independent prognostic factors. CONCLUSION: Activation of components of MAPK signaling pathway is associated with overall survival of patients with gliomas, thereby suggesting that the MAPK intermediates seem to play a critical role in the biologic behavior of gliomas. Further studies are needed to clarify whether these factors merit to be considered as potential therapeutic targets in future clinical trials.

[130]

**TÍTULO / TITLE:** - Pro-Surfactant Protein B as a Biomarker for Lung Cancer Prediction.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 18.

- Enlace al texto completo (gratis o de pago) [1200/JCO.2013.50.6105](#)

**AUTORES / AUTHORS:** - Sin DD; Tammemagi CM; Lam S; Barnett MJ; Duan X; Tam A; Auman H; Feng Z; Goodman GE; Hanash S; Taguchi A

**INSTITUCIÓN / INSTITUTION:** - Don D. Sin, Stephen Lam, and Anthony Tam, University of British Columbia; Don D. Sin and Anthony Tam, Institute of Heart and Lung Health, James Hogg Research Center, St. Paul's Hospital; Stephen Lam and Xiaobo Duan, British Columbia Cancer Agency, Vancouver, British Columbia; C. Martin Tammemagi, Brock University, St. Catharines, Ontario, Canada; Matt J. Barnett, Ziding Feng, and Gary E. Goodman, Fred Hutchinson Cancer Research Center, Seattle, WA; Heidi Auman, Canary Foundation, Palo Alto, CA; and Ziding Feng, Samir Hanash, and Ayumu Taguchi, University of Texas MD Anderson Cancer Center, Houston, TX.

**RESUMEN / SUMMARY:** - PURPOSE: Preliminary studies have identified pro-surfactant protein B (pro-SFTPb) to be a promising blood biomarker for non-small-cell lung cancer. We conducted a study to determine the independent predictive potential of pro-SFTPb in identifying individuals who are subsequently diagnosed with lung cancer. PATIENTS AND METHODS: Pro-SFTPb levels were measured in 2,485 individuals, who enrolled onto the Pan-Canadian Early Detection of Lung Cancer Study by using plasma sample collected at the baseline visit. Multivariable logistic regression models were used to evaluate the predictive ability of pro-SFTPb in addition to known lung cancer risk factors. Calibration and discrimination were evaluated, the latter by an area under the receiver operating characteristic curve (AUC). External validation was performed with samples collected in the Carotene and Retinol Efficacy Trial (CARET) participants using a case-control study design. RESULTS: Adjusted for age, sex, body mass index, personal history of cancer, family history of lung cancer, forced expiratory volume in one second percent predicted, average number of cigarettes smoked per day, and smoking duration, pro-SFTPb (log transformed) had an odds ratio of 2.220 (95% CI, 1.727 to 2.853; P < .001). The AUCs of the full model with and without pro-SFTPb were 0.741 (95% CI, 0.696 to 0.783) and 0.669 (95% CI, 0.620 to 0.717; difference in AUC P < .001). In the CARET Study, the use of pro-SFTPb yielded an

AUC of 0.683 (95% CI, 0.604 to 0.761). CONCLUSION: Pro-SFTPB in plasma is an independent predictor of lung cancer and may be a valuable addition to existing lung cancer risk prediction models.

[131]

**TÍTULO / TITLE:** - Molecular Pathways: Targeting Inhibitor of Apoptosis Proteins in Cancer-From Molecular Mechanism to Therapeutic Application.

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

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

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0227](#)

**AUTORES / AUTHORS:** - Fulda S

**INSTITUCIÓN / INSTITUTION:** - Institute for Experimental Cancer Research in Pediatrics, Goethe-University Frankfurt.

**RESUMEN / SUMMARY:** - Inhibitor of Apoptosis (IAP) proteins play a critical role in the control of survival and cell death by regulating key signaling events such as caspase activation and NF-kappaB signaling. Since aberrantly high expression of IAP proteins represents a frequent oncogenic event in human cancers, therapeutic targeting of IAP proteins is considered as a promising approach. Several small-molecule pharmacological inhibitors of IAP proteins that mimic the binding domain of the endogenous IAP antagonist second mitochondrial activator of caspases (Smac) to IAP proteins have been developed over the last years. IAP antagonists have been shown in various preclinical cancer models to either directly initiate cell death or, alternatively, to prime cancer cells for cytotoxic therapies by lowering the threshold for cell death induction. IAP antagonists (i.e. GDC-0917/CUDC-427, LCL161, AT-406, HGS1029 and TL32711) are currently under evaluation in early clinical trials alone or in combination regimens. Thus, the concept to therapeutically target IAP proteins in human cancer has in principle been successfully transferred into a clinical setting and warrants further evaluation as a treatment approach.

[132]

**TÍTULO / TITLE:** - Pan-mTOR inhibitor AZD8055 primes rhabdomyosarcoma cells for ABT-737-induced apoptosis by downregulating Mcl-1.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.495986](#)

**AUTORES / AUTHORS:** - Preuss E; Hugle M; Reimann R; Schlecht M; Fulda S

**INSTITUCIÓN / INSTITUTION:** - Institute for Experimental Cancer Research, Germany.

**RESUMEN / SUMMARY:** - The PI3K/mTOR pathway is often aberrantly activated in rhabdomyosarcoma (RMS) and represents a promising therapeutic target. Recent evaluation of AZD8055, an ATP-competitive mTOR inhibitor, by the Preclinical Pediatric Testing Program (PPTP) showed in vivo antitumor activity against childhood solid tumors including RMS. Therefore, in the present study we searched for AZD8055-based combination therapies. Here, we identify a new synergistic lethality of AZD8055 together with ABT-737, a BH3 mimetic that antagonizes Bcl-2, Bcl-XL and Bcl-w but not Mcl-1. AZD8055 and ABT-737 cooperate to induce apoptosis in alveolar and

embryonal RMS cells in a highly synergistic fashion (combination index <0.2). Synergistic induction of apoptosis by AZD8055 and ABT-737 is confirmed on the molecular level, as AZD8055 and ABT-737 cooperate to trigger loss of mitochondrial membrane potential, activation of caspases and caspase-dependent apoptosis that is blocked by the pan-caspase inhibitor zVAD.fmk. Similar to AZD8055, the PI3K/mTOR inhibitor NVP-BE2235 the PI3K inhibitor NVP-BKM120 and Akt inhibitor synergize with ABT-737 to trigger apoptosis, whereas no cooperativity is found for the mTORC1 inhibitor RAD001. Interestingly, molecular studies reveal a correlation between the ability of different PI3K/mTOR inhibitors to potentiate ABT-737-induced apoptosis and to suppress Mcl-1 protein levels. Importantly, knockdown of Mcl-1 increases ABT-737-induced apoptosis similar to AZD8055/ABT-737 cotreatment. This indicates that AZD8055-mediated suppression of Mcl-1 protein plays an important role in the synergistic drug interaction. By identifying a novel synergistic interaction of AZD8055 and ABT-737, our findings have important implications for the development of molecular targeted therapies for RMS.

[133]

**TÍTULO / TITLE:** - Prognostic role of microRNA polymorphisms in patients with advanced esophageal squamous cell carcinoma receiving platinum-based chemotherapy.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 28.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2364-x](#)

**AUTORES / AUTHORS:** - Wu C; Li M; Hu C; Duan H

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, Zhongshan Hospital affiliated to Xiamen University, Fujian, 361004, China.

**RESUMEN / SUMMARY:** - PURPOSE: MicroRNA (miRNA) polymorphisms contribute to cancer susceptibility and prognosis. The aim of this study was to evaluate the effects of miRNA polymorphisms on clinical outcomes in patients with advanced esophageal squamous cell carcinoma (ESCC) treated with platinum-based chemotherapy. METHODS: Five polymorphisms (miR-146a rs2910164, miR-196a2 rs11614913, miR-100 rs1834306, miR-125a rs12976445 and miR-26a1 rs7372209) were genotyped in 378 patients with advanced ESCC recruited at Zhongshan Hospital. The associations between genotypes and drug response, toxicity, and overall survival were analyzed. RESULTS: miR-146a rs2910164 was significantly associated with an increased risk of severe hematological toxicity [odds ratio = 0.374, 95 % confidence interval (CI) 0.171-0.819, P = 0.014]. The TT genotypes of both miR-196a2 rs11614913 and miR-125a rs12976445 were associated with worse survival [hazard ratio (HR) = 1.552, 95 % CI 1.112-2.165, P = 0.010; HR = 2.171, 95 % CI 1.173-4.017, P = 0.014, respectively]. Combined analysis revealed a 4.073-fold increased risk of death in patients carrying two unfavorable genotypes (P = 0.002). CONCLUSIONS: Taken together, these findings indicate that miRNA polymorphisms may predict prognosis in advanced ESCC patients receiving platinum-based chemotherapy.

[134]

**TÍTULO / TITLE:** - Prognostic Significance of Metastasis-Related microRNAs in Early Breast Cancer Patients with a Long Follow-up.

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

**REVISTA / JOURNAL:** - Clin Chem. 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1373/clinchem.2013.210542](http://dx.doi.org/10.1373/clinchem.2013.210542)

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**RESUMEN / SUMMARY:** - BACKGROUND: Stability of microRNAs (miRNAs) in formalin-fixed paraffin-embedded (FFPE) tissues enables their reliable analysis in archived FFPE tissue samples, which are an invaluable source for the evaluation of novel biomarkers. Especially in breast cancer, for which late relapses occur in many cases, analysis of miRNAs in FFPE tissues holds great potential, because it can lead to the discovery of novel biomarkers suitable for future routine clinical diagnostics for breast cancer. We investigated the prognostic significance of 6 metastasis-related miRNAs that can critically regulate various stages of migration and invasion and play critical roles in the multistep metastatic process. METHODS: We quantified the expression of 6 mature miRNAs (namely miR-21, miR-205, miR-10b, miR-210, miR-335, and let-7a-) by reverse-transcription quantitative PCR in FFPE tissues of 84 patients with early breast cancer and a long follow-up and 13 cancer-free breast tissue FFPE samples that were used as the control group. We further correlated individual miRNA over- or underexpression with the disease-free interval (DFI) and overall survival (OS). RESULTS: Univariate analysis revealed that both miR-21 and miR-205 were significantly associated with DFI and only miR-205 with OS. Multivariate analysis demonstrated that miR-205 and miR-21 were independent factors associated with early disease relapse, whereas only miR-205 overexpression was associated with OS. CONCLUSIONS: Our results clearly indicate that deregulation of metastasis-associated miRNAs in primary tumors is associated with clinical outcome in patients with early breast cancer and can differentiate patients with higher risk in well-characterized subgroups.

[135]

**TÍTULO / TITLE:** - Activation of proteinase-activated receptor 2 prevents apoptosis of lung cancer cells.

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

**REVISTA / JOURNAL:** - Cancer Invest. 2013 Nov;31(9):578-81. doi: 10.3109/07357907.2013.845674. Epub 2013 Oct 18.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.845674](http://dx.doi.org/10.3109/07357907.2013.845674)

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**RESUMEN / SUMMARY:** - The therapeutics of lung cancer (LC) is unsatisfactory. The pathogenesis of LC remains unclear. Protease-activated receptors (PAR) are involved in the immunoregulation. The present study aims to investigate the activation of PAR2 in regulation of the expression of EGFR and apoptosis of LC cells. The results showed

that exposure to tryptase increased EGFR expression in A549 cells and suppressed the cell apoptosis. Tryptase also decreased the expression of Bax and increased Bcl-xL levels in A549 cells. We conclude that activation of PAR2 by tryptase can decrease the ratio of Bax/Bcl-xL and reduce the LC cell line, A549 cells, and apoptosis.

[136]

**TÍTULO / TITLE:** - The thiol proteinase inhibitor E-64-d ameliorates amyloid-beta-induced reduction of sAPPalpha secretion by reversing ceramide-induced protein kinase C down-regulation in SH-SY5Y neuroblastoma cells.

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

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Nov 8;441(1):256-61. doi: 10.1016/j.bbrc.2013.10.045. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.10.045](#)

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**RESUMEN / SUMMARY:** - In Alzheimer's disease (AD), enhancing alpha-secretase processing of amyloid precursor protein (APP) is an important pathway to decrease neurotoxic amyloid beta (Abeta) secretion. The alpha-secretase is reported to be regulated by protein kinase C (PKC) and various endogenous proteins or cell surface receptors. In this report, we first examined whether Abeta reduces alpha-secretase activity, and showed that Abeta peptide 1-40 (0.001 and 0.01μM) reduced the secretion of soluble amyloid precursor protein alpha (sAPPalpha) in carbachol-stimulated SH-SY5Y neuroblastoma cells. E-64-d (3μM), which is a potent calpain inhibitor that prevents PKC degradation, ameliorated the Abeta-induced reduction of sAPPalpha secretion. In addition, we observed that Abeta significantly enhanced ceramide production by activating neutral sphingomyelinase. The cell-permeable ceramide analog, C2-ceramide (1μg/mL), also reduced sAPPalpha secretion, and in addition, E-64-d eliminated the observed decrease of sAPPalpha secretion. C2-ceramide induced down-regulation of PKC-alpha, -beta1, and -beta2 isozymes in SH-SY5Y cells. These findings suggest that ceramide may play an important role in sAPPalpha processing by modulating PKC activity.

[137]

**TÍTULO / TITLE:** - Chromosome 1q21 gains confer inferior outcomes in multiple myeloma treated with bortezomib but copy number variation and percentage of plasma cells involved have no prognostic value.

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

**REVISTA / JOURNAL:** - Haematologica. 2013 Nov 8.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.088211](#)

**AUTORES / AUTHORS:** - An G; Xu Y; Shi L; Zhong S; Deng S; Xie Z; Sui W; Zhan F; Qiu L

**INSTITUCIÓN / INSTITUTION:** - CAMS and PUMC, China;

**RESUMEN / SUMMARY:** - Abstract Chromosome 1q21 aberrations have not been implemented into the routine clinical test yet, and their effect in multiple myeloma is still under investigation. The prognostic value of copy number variation and percentage of plasma cells involved remained unclear. In the present study, we analyzed the prognostic value of 1q21 in a series of 290 cases of newly diagnosed multiple myeloma treated in a prospective, nonrandomized clinical trial (BDH 2008/02). We found that incidence of 1q21 aberration increased at relapse, but its copy numbers and proportion of cells involved did not change. Gains of 1q21 had no impact on survival in patients receiving thalidomide-based treatment, but conferred a significant inferior prognosis in patients under bortezomib-based chemotherapy and was an independent adverse prognostic factor for progression free survival (HR 3.831 [95% CI 2.125-6.907],  $p < 0.001$ ) and overall survival (HR 3.245 [95% CI 1.555-6.773],  $p = 0.002$ ). Strikingly, our results showed that the copy number variation and clone size harboring 1q21 gains carried no additional prognostic value and patients with 1q21 gains did not benefit from regimens incorporating bortezomib significantly. Our results indicate that three copies of 1q21 gains and 20% of plasma cells with this abnormality were enough to confer bortezomib resistance. Therefore, chromosome 1q21 gains should be considered a high-risk feature in multiple myeloma receiving bortezomib therapy.

[138]

**TÍTULO / TITLE:** - A prognostic DNA methylation signature for stage I non-small-cell lung cancer.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 10;31(32):4140-7. doi: 10.1200/JCO.2012.48.5516. Epub 2013 Sep 30.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2012.48.5516](#)

**AUTORES / AUTHORS:** - Sandoval J; Mendez-Gonzalez J; Nadal E; Chen G; Carmona FJ; Sayols S; Moran S; Heyn H; Vizoso M; Gomez A; Sanchez-Cespedes M; Assenov Y; Muller F; Bock C; Taron M; Mora J; Muscarella LA; Liloglou T; Davies M; Pollan M; Pajares MJ; Torre W; Montuenga LM; Brambilla E; Field JK; Roz L; Lo Iacono M; Scagliotti GV; Rosell R; Beer DG; Esteller M

**INSTITUCIÓN / INSTITUTION:** - Juan Sandoval, Jesus Mendez-Gonzalez, F. Javier Carmona, Sergi Sayols, Sebastian Moran, Holger Heyn, Miguel Vizoso, Antonio Gomez, Montse Sanchez-Cespedes, and Manel Esteller, Bellvitge Biomedical Research Institute; Josefina Mora, Hospital de la Santa Creu i Sant Pau; Manel Esteller, University of Barcelona and Institutio Catalana de Recerca i Estudis Avancats, Barcelona; Miquel Taron and Rafael Rosell, Catalan Institute of Oncology, Badalona, Catalonia; Marina Pollan, Instituto de Salud Carlos III, Madrid; Maria J. Pajares and Luis M. Montuenga, University of Navarra; Wenceslao Torre, Clinica University de Navarra, Pamplona, España; Ernest Nadal, Guoan Chen, and David G. Beer, University of Michigan Medical School, Ann Arbor, MI; Yassen Assenov and Fabian Muller, Max Planck Institute, Saarbrucken, Germany; Christoph Bock, Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria; Lucia A. Muscarella, Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Triantafillos Liloglou, Michael Davies, and John K. Field, The University of Liverpool Cancer Research Centre, Liverpool, United Kingdom; Elisabeth Brambilla, Centre Hospitalier Universitaire A Michallon,

Grenoble, France; Luca Roz, IRCCS Foundation National Cancer Institute, Milan; Marco Lo Iacono and Giorgio V. Scagliotti, University of Torino, Orbassano (Torino), Italy.

**RESUMEN / SUMMARY:** - PURPOSE: Non-small-cell lung cancer (NSCLC) is a tumor in which only small improvements in clinical outcome have been achieved. The issue is critical for stage I patients for whom there are no available biomarkers that indicate which high-risk patients should receive adjuvant chemotherapy. We aimed to find DNA methylation markers that could be helpful in this regard. PATIENTS AND METHODS: A DNA methylation microarray that analyzes 450,000 CpG sites was used to study tumoral DNA obtained from 444 patients with NSCLC that included 237 stage I tumors. The prognostic DNA methylation markers were validated by a single-methylation pyrosequencing assay in an independent cohort of 143 patients with stage I NSCLC. RESULTS: Unsupervised clustering of the 10,000 most variable DNA methylation sites in the discovery cohort identified patients with high-risk stage I NSCLC who had shorter relapse-free survival (RFS; hazard ratio [HR], 2.35; 95% CI, 1.29 to 4.28; P = .004). The study in the validation cohort of the significant methylated sites from the discovery cohort found that hypermethylation of five genes was significantly associated with shorter RFS in stage I NSCLC: HIST1H4F, PCDHGB6, NPBWR1, ALX1, and HOXA9. A signature based on the number of hypermethylated events distinguished patients with high- and low-risk stage I NSCLC (HR, 3.24; 95% CI, 1.61 to 6.54; P = .001). CONCLUSION: The DNA methylation signature of NSCLC affects the outcome of stage I patients, and it can be practically determined by user-friendly polymerase chain reaction assays. The analysis of the best DNA methylation biomarkers improved prognostic accuracy beyond standard staging.

[139]

**TÍTULO / TITLE:** - Gemtuzumab ozogamicin in combination with vorinostat and azacitidine in older patients with relapsed or refractory acute myeloid leukemia: a phase ½ study.

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

**REVISTA / JOURNAL:** - Haematologica. 2013 Oct 18.

●● [Enlace al texto completo \(gratis o de pago\) 3324/haematol.2013.096545](#)

**AUTORES / AUTHORS:** - Walter RB; Medeiros BC; Gardner KM; Orlowski KF; Gallegos L; Scott BL; Hendrie PC; Estey EH

**INSTITUCIÓN / INSTITUTION:** - USA;

**RESUMEN / SUMMARY:** - Epigenetic therapeutics such as the histone deacetylase inhibitor, vorinostat, and the DNA methyltransferase I inhibitor, azacitidine, enhance gemtuzumab ozogamicin efficacy in vitro. We therefore investigated vorinostat/azacitidine/gemtuzumab ozogamicin in 52 adults  $\geq 50$  years with acute myeloid leukemia requiring therapy for first relapse (remission duration  $\leq 12$  months) or primary refractory disease in a phase ½ trial. Vorinostat and gemtuzumab ozogamicin were escalated step-wise during the phase 1 portion of the trial. Vorinostat (400 mg/day orally from days 1-9), azacitidine (75 mg/m<sup>2</sup>/day intravenously or subcutaneously from days 1-7), and gemtuzumab ozogamicin (3 mg/m<sup>2</sup>/day intravenously on days 4 and 8) were identified as the maximum tolerated dose. Among the 43 patients treated at this dose, 10 achieved a complete remission and 8 achieved a complete remission with incomplete blood count recovery, for an overall response

rate of 41.9% (exact 95% confidence interval: 27.0-57.9%); 4 of these 18 patients (2 each with complete remission and complete remission with incomplete blood count recovery) had persistence of minimal residual disease by flow cytometry at the time of best response. Four patients died within 28 days of treatment initiation. Median overall survival for the 18 patients achieving complete remission/complete remission with incomplete blood count recovery was significantly longer than for those 21 patients who failed therapy but lived at least 29 days after treatment initiation (224.5 [range 70-798]) vs. 95 [36-900] days; P=0.0023). These data indicate that vorinostat/azacitidine/gemtuzumab ozogamicin has activity in this difficult-to-treat acute myeloid leukemia patient subset. This trial was registered at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (NCT00895934).

[140]

**TÍTULO / TITLE:** - Neutropenia management and granulocyte colony-stimulating factor use in patients with solid tumours receiving myelotoxic chemotherapy-findings from clinical practice.

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

**REVISTA / JOURNAL:** - Support Care Cancer. 2013 Oct 24.

- [Enlace al texto completo \(gratis o de pago\) 1007/s00520-013-2021-2](#)

**AUTORES / AUTHORS:** - Krzemieniecki K; Sevela P; Erdkamp F; Smakal M; Schwenkglens M; Puertas J; Trojan A; Szabo Z; Bendall K; Maenpaa J

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**RESUMEN / SUMMARY:** - **PURPOSE:** Clinical practice adherence to current guidelines that recommend primary prophylaxis (PP) with granulocyte colony-stimulating factors (G-CSFs) for patients at high ( $\geq 20\%$ ) overall risk of febrile neutropenia (FN) was evaluated. **METHODS:** Adult patients with breast cancer, non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), or ovarian cancer were enrolled if myelotoxic chemotherapy was planned, and they had an investigator-assessed overall FN risk  $\geq 20\%$ . The primary outcome was FN incidence. **RESULTS:** In total, 1,347 patients were analysed (breast cancer, n = 829; NSCLC, n = 224; SCLC, n = 137; ovarian cancer, n = 157). Patients with breast cancer exhibited fewer individual FN risk factors than patients with other cancers and were far more likely to have received a high-FN-risk chemotherapy regimen. However, a substantial proportion of all patients (45-80% across tumour types) did not receive G-CSF PP in alignment with investigator risk assessment and guideline recommendations. FN occurred in 127 patients overall (9%, 95% confidence interval (CI) 8-11%), and incidence was higher in SCLC (15%) than other tumour types (8% in ovarian and NSCLC, 9% in breast cancer). A post hoc analysis of G-CSF use indicated that G-CSF prophylaxis was not given within the recommended timeframe after chemotherapy (within 1-3 days) or was not continued across all cycles in 39% of patients. **CONCLUSIONS:** FN risk assessment was predominantly based on clinical judgement and individual risk factors, and guidelines regarding G-CSF PP for patients at high FN risk were not consistently followed. Improved education of physicians may enable more fully informed neutropenia management in patients with solid tumours.

[141]

**TÍTULO / TITLE:** - The histone deacetylase inhibitor abexinostat induces cancer stem cells differentiation in breast cancer with low xist expression.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Dec 1;19(23):6520-31. doi: 10.1158/1078-0432.CCR-13-0877. Epub 2013 Oct 18.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0877](#)

**AUTORES / AUTHORS:** - Salvador MA; Wicinski J; Cabaud O; Toiron Y; Finetti P; Josselin E; Lelievre H; Kraus-Berthier L; Depil S; Bertucci F; Collette Y; Birnbaum D; Charafe-Jauffret E; Ginestier C

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Institut national de la sante et de la recherche medicale (INSERM), CRCM, U1068, Laboratoire d'Oncologie Moleculaire; Departement de Biopathologie, Institut Paoli-Calmettes; Aix Marseille Universite, F-13007; CNRS, CRCM, 7258; INSERM, CRCM, U1068, TrGET, Marseille; and Institut de Recherches Internationales Servier, Paris, France.

**RESUMEN / SUMMARY:** - PURPOSE: Cancer stem cells (CSC) are the tumorigenic cell population that has been shown to sustain tumor growth and to resist conventional therapies. The purpose of this study was to evaluate the potential of histone deacetylase inhibitors (HDACi) as anti-CSC therapies. EXPERIMENTAL DESIGN: We evaluated the effect of the HDACi compound abexinostat on CSCs from 16 breast cancer cell lines (BCL) using ALDEFLUOR assay and tumorsphere formation. We performed gene expression profiling to identify biomarkers predicting drug response to abexinostat. Then, we used patient-derived xenograft (PDX) to confirm, in vivo, abexinostat treatment effect on breast CSCs according to the identified biomarkers. RESULTS: We identified two drug-response profiles to abexinostat in BCLs. Abexinostat induced CSC differentiation in low-dose sensitive BCLs, whereas it did not have any effect on the CSC population from high-dose sensitive BCLs. Using gene expression profiling, we identified the long noncoding RNA Xist (X-inactive specific transcript) as a biomarker predicting BCL response to HDACi. We validated that low Xist expression predicts drug response in PDXs associated with a significant reduction of the breast CSC population. CONCLUSIONS: Our study opens promising perspectives for the use of HDACi as a differentiation therapy targeting the breast CSCs and identified a biomarker to select patients with breast cancer susceptible to responding to this treatment. Clin Cancer Res; 19(23); 6520-31. ©2013 AACR.

[142]

**TÍTULO / TITLE:** - A phase II study of bevacizumab and high-dose interleukin-2 in patients with metastatic renal cell carcinoma: a Cytokine Working Group (CWG) study.

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

**REVISTA / JOURNAL:** - J Immunother. 2013 Nov-Dec;36(9):490-5. doi: 10.1097/CJI.0000000000000003.

●● Enlace al texto completo (gratis o de pago) [1097/CJI.0000000000000003](#)

**AUTORES / AUTHORS:** - Dandamudi UB; Ghebremichael M; Sosman JA; Clark JI; McDermott DF; Atkins MB; Dutcher JP; Urba WJ; Regan MM; Puzanov I; Crocenzi TS; Curti BD; Vaishampayan UN; Crosby NA; Margolin KA; Ernstoff MS

**INSTITUCIÓN / INSTITUTION:** - \*Dartmouth Hitchcock Medical Center, Lebanon, NH daggerDana-Farber Cancer Institute, Harvard School of Public Health parallelBeth Israel Deaconess Medical Center double daggerdouble daggerDana-Farber Cancer Institute, Harvard Medical School, Boston, MA double daggerVanderbilt University Medical Center, Nashville, TN section signLoyola University Medical Center, Maywood, IL paragraph signGeorgetown Lombardi Comprehensive Cancer Center, Washington, DC #St. Luke's Roosevelt Hospital Center, New York, NY \*\*Earle A. Chiles Research Institute daggerdaggerProvidence Cancer Center, Portland, OR section sign section signDepartment of Oncology, Wayne State University, Karmanos Cancer Institute, Detroit, MI parallel parallelDivision of Oncology, Department of Medicine, University of Washington, Seattle Cancer Care Alliance, Seattle, WA.

**RESUMEN / SUMMARY:** - Overexpression of vascular endothelial growth factor in renal cell carcinoma (RCC) leads to angiogenesis, tumor progression, and inhibition of immune function. We conducted the first phase II study to estimate the efficacy and safety of bevacizumab with high-dose interleukin-2 (IL-2) therapy in patients with metastatic RCC. Eligible patients had predominantly clear cell metastatic RCC, measurable disease, a Karnofsky Performance Status of  $\geq 80\%$ , and adequate end-organ function. IL-2 (600,000 IU/kg) was infused intravenously every 8 hours (maximum 28 doses) during two 5-day cycles on days 1 and 15 of each 84-day course. Bevacizumab (10 mg/kg) was infused intravenously every 2 weeks beginning 2 weeks before initiating IL-2. Fifty of 51 eligible patients from 8 centers were enrolled. Median progression-free survival (PFS) was 11.2 months (90% confidence interval, 5.7-17.7), and 2-year PFS was 18% (90% confidence interval, 8%-27%). Responses included 4 complete (8%) and 11 partial (22%) responses. Toxicities did not exceed those expected from each agent alone. Combining IL-2 plus bevacizumab is feasible, with a response rate and PFS at least as high as reported previously for the single agents. The regimen did not appear to enhance the rate of durable major responses over that of IL-2 alone.

[143]

**TÍTULO / TITLE:** - miRNA27a is a biomarker for predicting chemosensitivity and prognosis in metastatic or recurrent gastric cancer patients receiving first-line chemotherapy.

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

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 Oct 7. doi: 10.1002/jcb.24689.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24689](#)

**AUTORES / AUTHORS:** - Huang D; Wang H; Liu R; Li H; Ge S; Bai M; Deng T; Yao G; Ba Y

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Huanhuxi Rd., Tiyuanbei, Hexi District, Tianjin, 300060, PR China.

**RESUMEN / SUMMARY:** - We previously identified five miRNAs (miR-1, miR-20a, miR-27a, miR-34a and miR-423-5p) that are up-regulated in gastric cancer. The goal of this study was to investigate the value of these miRNAs as potential biomarkers for predicting chemosensitivity and prognosis in metastatic or recurrent gastric cancer patients who received first-line chemotherapy. A total of 82 patients with metastatic or

recurrent GC receiving first-line chemotherapy were included in our study. The expression levels of the five miRNAs were evaluated using hydrolysis probe-based stem-loop quantitative reverse transcription polymerase chain reaction (qRT-PCR) in individual samples before first-line chemotherapy. Patients receiving first-line chemotherapy with fluoropyrimidine combined with oxaliplatin or paclitaxel were chosen for the chemosensitivity analysis. The relationships between expression of the five-miRNAs and clinicopathological parameters, response to chemotherapy and prognosis were analysed statistically. Patients with higher miRNA1 expression levels tended to have a higher rate of liver metastasis, and higher miRNA34a expression levels occurred more frequently in males ( $P = 0.022$ ). The expression of the remaining three miRNAs showed no obvious relationship to any of the clinicopathological features. The partial response rates of the patients with high miRNA1 expression and low miRNA1 expression were 11.1% and 23.1%, respectively ( $P = 0.048$ ). Similar results were observed for miRNA27a (the partial response rate was 7.7% vs 25.9%,  $P = 0.018$ ). Patients with up-regulated miRNA27a expression had a significantly worse overall survival (OS) than patients with lower miRNA27a expression ( $P = 0.024$ ). In patients with MRGC, miRNA27a is a potential biomarker for predicting resistance to fluoropyrimidine-based chemotherapy and a novel prognostic marker for gastric cancer. *J. Cell. Biochem.* © 2013 Wiley Periodicals, Inc.

[144]

**TÍTULO / TITLE:** - A phase 1 study of everolimus + weekly cisplatin + intensity modulated radiation therapy in head-and-neck cancer.

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

**REVISTA / JOURNAL:** - *Int J Radiat Oncol Biol Phys.* 2013 Nov 1;87(3):479-86. doi: 10.1016/j.ijrobp.2013.06.2043.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ijrobp.2013.06.2043](#)

**AUTORES / AUTHORS:** - Fury MG; Lee NY; Sherman E; Ho AL; Rao S; Heguy A; Shen R; Korte S; Lisa D; Ganly I; Patel S; Wong RJ; Shaha A; Shah J; Haque S; Katabi N; Pfister DG

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Head and Neck Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York; Department of Medicine, Weill Cornell Medical College, New York, New York.

**RESUMEN / SUMMARY:** - **PURPOSE:** Elevated expression of eukaryotic protein synthesis initiation factor 4E (eIF4E) in histologically cancer-free margins of resected head and neck squamous cell carcinomas (HNSCCs) is mediated by mammalian target of rapamycin complex 1 (mTORC1) and has been associated with increased risk of disease recurrence. Preclinically, inhibition of mTORC1 with everolimus sensitizes cancer cells to cisplatin and radiation. **METHODS AND MATERIALS:** This was single-institution phase 1 study to establish the maximum tolerated dose of daily everolimus given with fixed dose cisplatin (30 mg/m<sup>2</sup>) weekly x 6) and concurrent intensity modulated radiation therapy for patients with locally and/or regionally advanced head-and-neck cancer. The study had a standard 3 + 3 dose-escalation design. **RESULTS:** Tumor primary sites were oral cavity (4), salivary gland (4), oropharynx (2), nasopharynx (1), scalp (1), and neck node with occult primary (1). In 4 of 4 cases in which resected HNSCC surgical pathology specimens were available for immunohistochemistry, elevated expression of eIF4E was observed in the cancer-free

margins. The most common grade  $\geq 3$  treatment-related adverse event was lymphopenia (92%), and dose-limiting toxicities (DLTs) were mucositis (n=2) and failure to thrive (n=1). With a median follow up of 19.4 months, 2 patients have experienced recurrent disease. The maximum tolerated dose was everolimus 5 mg/day. CONCLUSIONS: Head-and-neck cancer patients tolerated everolimus at therapeutic doses (5 mg/day) given with weekly cisplatin and intensity modulated radiation therapy. The regimen merits further evaluation, especially among patients who are status post resection of HNSCCs that harbor mTORC1-mediated activation of eIF4E in histologically negative surgical margins.

[145]

**TÍTULO / TITLE:** - Arctigenin, a dietary phytoestrogen, induces apoptosis of estrogen receptor-negative breast cancer cells through the ROS/p38 MAPK pathway and epigenetic regulation.

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

**REVISTA / JOURNAL:** - Free Radic Biol Med. 2013 Oct 17;67C:159-170. doi: 10.1016/j.freeradbiomed.2013.10.004.

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

[1016/j.freeradbiomed.2013.10.004](http://1016/j.freeradbiomed.2013.10.004)

**AUTORES / AUTHORS:** - Hsieh CJ; Kuo PL; Hsu YC; Huang YF; Tsai EM; Hsu YL

**INSTITUCIÓN / INSTITUTION:** - Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan; Department of Chinese Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan.

**RESUMEN / SUMMARY:** - This study investigates the anticancer effect of arctigenin (ATG), a natural lignan product of *Arctium lappa* L., in human breast cancer MDA-MB-231 cells. Results indicate that ATG inhibits MDA-MB-231 cell growth by inducing apoptosis in vitro and in vivo. ATG triggers the mitochondrial caspase-independent pathways, as indicated by changes in Bax/Bcl-2 ratio, resulting in AIF and EndoG nuclear translocation. ATG increased cellular reactive oxygen species (ROS) production by increasing p22phox/NADPH oxidase 1 interaction and decreasing glutathione level. ATG clearly increases the activation of p38 MAPK, but not JNK and ERK1/2. Antioxidant EUK-8, a synthetic catalytic superoxide and hydrogen peroxide scavenger, significantly decreases ATG-mediated p38 activation and apoptosis. Blocking p38 with a specific inhibitor suppresses ATG-mediated Bcl-2 downregulation and apoptosis. Moreover, ATG activates ATF-2, a transcription factor activated by p38, and then upregulates histone H3K9 trimethylation in the Bcl-2 gene promoter region, resulting in Bcl-2 downregulation. Taken together, the results demonstrate that ATG induces apoptosis of MDA-MB-231 cells via the ROS/p38 MAPK pathway and epigenetic regulation of Bcl-2 by upregulation of histone H3K9 trimethylation.

[146]

**TÍTULO / TITLE:** - Identifying arsenic trioxide (ATO) functions in leukemia cells by using time series gene expression profiles.

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

**REVISTA / JOURNAL:** - Gene. 2013 Nov 18. pii: S0378-1119(13)01512-6. doi: 10.1016/j.gene.2013.10.072.

●● Enlace al texto completo (gratis o de pago) [1016/j.gene.2013.10.072](http://1016/j.gene.2013.10.072)

**AUTORES / AUTHORS:** - Yang H; Lin S; Cui J

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, 4<sup>th</sup> Hospital of Harbin Medical University, Harbin 150001, China.

**RESUMEN / SUMMARY:** - Arsenic trioxide (ATO) is presently the most active single agent in the treatment of acute promyelocytic leukemia (APL). In order to explore the molecular mechanism of ATO in leukemia cells with time series, we adopted bioinformatics strategy to analyze expression changing patterns and changes in transcription regulation modules of time series genes filtered from Gene Expression Omnibus database (GSE24946). We totally screened out 1847 time series genes for subsequent analysis. The KEGG (Kyoto encyclopedia of genes and genomes) pathways enrichment analysis of these genes showed that oxidative phosphorylation and ribosome were the top 2 significantly enriched pathways. STEM software was employed to compare changing patterns of gene expression with assigned 50 expression patterns. We screened out 7 significantly enriched patterns and 4 tendency charts of time series genes. The result of Gene Ontology showed that functions of times series genes mainly distributed in profiles 41, 40, 39 and 38. Seven genes with positive regulation of cell adhesion function were enriched in profile 40, and presented the same first increased model then decreased model as profile 40. The transcription module analysis showed that they mainly involved in oxidative phosphorylation pathway and ribosome pathway. Overall, our data summarized the gene expression changes in ATO treated K562-r cell lines with time and suggested that time series genes mainly regulated cell adhesive. Furthermore, our result may provide theoretical basis of molecular biology in treating acute promyelocytic leukemia.

[147]

**TÍTULO / TITLE:** - Phase I dose-escalation study of oral vinflunine in combination with erlotinib in pre-treated and unselected EGFR patients with locally advanced or metastatic non-small-cell lung cancer.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2342-3](http://1007/s00280-013-2342-3)

**AUTORES / AUTHORS:** - Krzakowski M; Bennouna J; Dansin E; Kowalski D; Hirt S; Penel N; Favrel S; Tourani JM

**INSTITUCIÓN / INSTITUTION:** - Institute of Oncology, Warsaw, Poland, [maciekk@coi.waw.pl](mailto:maciekk@coi.waw.pl).

**RESUMEN / SUMMARY:** - BACKGROUND: Erlotinib, the epidermal growth factor receptor tyrosine kinase inhibitor, and the intra-venous vinflunine vinca alkaloid microtubule inhibitor have been shown to be effective in the setting of non-small-cell lung cancer (NSCLC) palliative patients with acceptable toxicities. This phase I study was conducted to determine the maximal tolerated dose (MTD) and the safety of an all-oral combination. A potential pharmacokinetic drug-drug interaction was also investigated. PATIENTS AND METHODS: Patients with unresectable stage IIIB or stage IV NSCLC who failed one or two previous chemotherapy regimens were treated with flat doses of oral vinflunine from day 1 to day 5 and from day 8 to day 12 every 3 weeks and erlotinib daily on a continuous basis. The dose levels of vinflunine/erlotinib were 95/100, 115/100, 115/150 and 135/100 mg. RESULTS: Thirty patients were

enrolled. The recommended dose was 115/150 mg and the MTD 135/100 mg. Dose-limiting toxicities included grade 3 febrile neutropenia (1 patient) and related death (1 patient). Non-haematologic grade 3/4 toxicities included fatigue, condition aggravated, hypokalaemia, tumour pain, acneiform dermatitis, diarrhoea, hyperbilirubinaemia and pulmonary haemorrhage, in one patient each. Of 25 patients evaluable for tumour response, 2 patients had partial response and 20 patients had stable disease. CONCLUSION: The recommended doses for oral vinflunine and erlotinib combination were, respectively, 115 mg/day from day 1 to day 5 and from day 8 to day 12 every 3 weeks and 150 mg/day. There was no mutual impact on pharmacokinetics. The combination was safe but evaluation in phase II is needed to further refine the activity and toxicity that can be expected with prolonged administration of this dose schedule.

[148]

**TÍTULO / TITLE:** - Molecular Pathways: Gene-environment interactions regulating dietary fiber induction of proliferation and apoptosis via butyrate for cancer prevention.

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

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

- [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-](#)

[2483](#)

**AUTORES / AUTHORS:** - Bultman SJ

**INSTITUCIÓN / INSTITUTION:** - Genetics, University of North Carolina.

**RESUMEN / SUMMARY:** - Gene-environment interactions are so numerous and biologically complicated that it can be challenging to understand their role in cancer. However, dietary fiber and colorectal cancer prevention may represent a tractable model system. Fiber is fermented by colonic bacteria into short-chain fatty acids such as butyrate. One molecular pathway that has emerged involves butyrate having differential effects depending on its concentration and the metabolic state of the cell. Low-moderate concentrations, which are present near the base of colonic crypts, are readily metabolized in the mitochondria to stimulate cell proliferation via energetics. Higher concentrations, which are present near the lumen, exceed the metabolic capacity of the colonocyte. Unmetabolized butyrate enters the nucleus and functions as a histone deacetylase (HDAC) inhibitor that epigenetically regulates gene expression to inhibit cell proliferation and induce apoptosis as the colonocytes exfoliate into the lumen. Butyrate may therefore play a role in normal homeostasis by promoting turnover of the colonic epithelium. Because cancerous colonocytes undergo the Warburg effect, their preferred energy source is glucose instead of butyrate. Consequently, even moderate concentrations of butyrate accumulate in cancerous colonocytes and function as HDAC inhibitors to inhibit cell proliferation and induce apoptosis. These findings implicate a bacterial metabolite with metaboloepigenetic properties in tumor suppression.

[149]

**TÍTULO / TITLE:** - Analysis of plasma cytokines and angiogenic factors in patients with pretreated urothelial cancer receiving Pazopanib: the role of circulating interleukin-8 to enhance the prognostic accuracy.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 14. doi: 10.1038/bjc.2013.719.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.719](http://dx.doi.org/10.1038/bjc.2013.719)

**AUTORES / AUTHORS:** - Necchi A; Pennati M; Zaffaroni N; Landoni E; Giannatempo P; Raggi D; Schwartz LH; Morosi C; Crippa F; Fare E; Nicolai N; Lanocita R; Sava T; Sacco C; Messina C; Ortega C; De Braud FG; Salvioni R; Daidone MG; Gianni AM; Mariani L

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Medical Oncology 2 Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian 1, Milan 20133, Italy.

**RESUMEN / SUMMARY:** - Background:Pazopanib achieved the end point of clinical activity in pretreated patients with urothelial cancer in a single-group, phase 2 trial. The objective was to identify biological predictors of clinical benefit to pazopanib in these patients.Methods:EDTA blood samples were collected at baseline (T0) and after 4 weeks (T1) of treatment, together with radiological imaging in all 41 patients to analyse plasma circulating angiogenic factor levels by multiplex ELISA plates. Changes from T0 to T1 in marker levels were matched with response with the covariance analysis. Univariable and multivariable analyses evaluated the association with overall survival (OS), adjusted for prespecified clinical variables. Net reclassification improvement (NRI) tested the performance of the recognised Cox model.Results:Increasing IL8T1 level associated with lower response probability at covariance analysis (P=0.010). Both IL8T0 (P=0.019) and IL8T1 (P=0.004) associated with OS and the prognostic model, including clinical variables and IL8T1 best-predicted OS after backward selection. The NRI for this model was 39%.When analysed as a time-varying covariate, IL8T1 level<80 pg ml<sup>-1</sup> portended significantly greater response ( approximately 80%) and 6-month OS ( approximately 60%) probability than level>=80.Conclusion:IL8-level changes during pazopanib allowed for a prognostic improvement and were associated with response probability.British Journal of Cancer advance online publication, 14 November 2013; doi:10.1038/bjc.2013.719 [www.bjcancer.com](http://www.bjcancer.com).

[150]

**TÍTULO / TITLE:** - Induction of p53 expression and apoptosis by a recombinant dual-target MDM2/MDMX inhibitory protein in wildtype p53 breast cancer cells.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):1935-42. doi: 10.3892/ijo.2013.2138. Epub 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2138](http://dx.doi.org/10.3892/ijo.2013.2138)

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**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Shaanxi, P.R. China.

**RESUMEN / SUMMARY:** - The tumor suppressor gene p53 is often inactivated in breast cancer cells due to gene mutation or overexpression of its repressors (such as murine double minute 2 and murine double minute X). Inhibitors of murine double minute 2 (MDM2) and murine double minute X (MDMX) could lead to tumor suppression by restoration of p53 activity and such an approach is a promising strategy for future control of breast cancer. This study aimed to investigate the feasibility of the recombinant MDM2 and MDMX inhibitory protein in control of breast cancer in vitro. A

cell-permeable dual-target MDM2/MDMX inhibitory protein was expressed in E. coli and incubated with p53 wildtype breast cancer cells. The data showed that this recombinant MDM2/MDMX inhibitory protein reduced the viability of MCF-7 and ZR-75-30 breast cancer cell lines and promoted cell cycle arrest and apoptosis by activation and stabilization of the p53 protein. Mechanistically, this MDM2/MDMX inhibitory protein increased the expression of p21, Bax and puma proteins, and inhibitory expression of MDM2 and MDMX proteins. This recombinant protein showed a better in vitro effect than that of nutlin-3alpha, a small molecule MDM2 inhibitor. The data further support the hypothesis that targeting of the p53 gene pathway could effectively control breast cancer.

[151]

**TÍTULO / TITLE:** - Changes in the plasma levels of cytokines/chemokines for predicting the response to chemoradiation therapy in rectal cancer patients.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):463-71. doi: 10.3892/or.2013.2857. Epub 2013 Nov 19.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2857](#)

**AUTORES / AUTHORS:** - Tada N; Tsuno NH; Kawai K; Murono K; Nirei T; Ishihara S; Sunami E; Kitayama J; Watanabe T

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology, University of Tokyo, Tokyo 113-0033, Japan.

**RESUMEN / SUMMARY:** - In the present study, we aimed to characterize the predictive value of cytokines/chemokines in rectal cancer (RC) patients receiving chemoradiation therapy (CRT). Blood samples were obtained pre- and post-CRT from 35 patients with advanced RC, who received neoadjuvant CRT followed by surgery, and the correlation between plasma levels of cytokines/chemokines and the response to CRT was analyzed. The pre-CRT levels of soluble CD40-ligand (sCD40L) and the post-CRT levels of chemokine ligand-5 (CCL-5) were significantly associated with the depth of tumor invasion and with venous invasion. In addition, a significant decrease in sCD40L and CCL-5, as well as in platelet counts, was associated with a favorable response to CRT. A significant correlation between pre-CRT platelet counts and sCD40L was observed in patients with a favorable response. By contrast, higher post-CRT interleukin (IL)-6 was associated with a poor response. Platelets, immune system and cancer cells, cross-linked through various cytokines/chemokines, appear to play an important role in the response to CRT, and by understanding their roles, new approaches for the improvement of the therapy might be proposed.

[152]

**TÍTULO / TITLE:** - ING4 regulates JWA in angiogenesis and their prognostic value in melanoma patients.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2842-52. doi: 10.1038/bjc.2013.670. Epub 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.670](#)

**AUTORES / AUTHORS:** - Lu J; Tang Y; Cheng Y; Zhang G; Yip A; Martinka M; Dong Z; Zhou J; Li G

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**RESUMEN / SUMMARY:** - Background: We previously showed that inhibitor of growth family member 4 (ING4) inhibits melanoma angiogenesis, and JWA suppresses the metastasis of melanoma cells. As angiogenesis is essential for tumour metastasis, further investigation of the function of ING4 and JWA in melanoma angiogenesis is needed, and their prognostic value are of great interest. Methods: Western blot, tube-formation assays and luciferase assays were used to investigate the correlation between ING4 and JWA in melanoma angiogenesis. JWA and integrin-linked kinase (ILK) expression was determined on a tissue microarray constructed from 175 biopsies. Results: ING4 promoted JWA expression by activating JWA promoter. Furthermore, the regulation of growth and tube formation of endothelial cells by ING4 was partially JWA dependent. Also, ING4 inhibited the ILK-induced angiogenesis signalling pathway via JWA. Moreover, reduced JWA, or increased ILK, expression was closely associated with 5-year disease-specific survival of melanoma patients (P=0.001 and 0.007, respectively). There was also a positive correlation between ING4 and JWA yet a negative correlation between ING4 and ILK. Importantly, their concomitant expressions were significantly related to 5-year survival of melanoma patients (P=0.002 and 0.003, respectively). Conclusion: JWA has an important role in ING4-regulated melanoma angiogenesis, and ING4/JWA/ILK are promising prognostic markers and may be used as anti-angiogenic therapeutic targets for melanoma.

[153]

**TÍTULO / TITLE:** - Human amniotic epithelial cells induce apoptosis of cancer cells: a new antitumor therapeutic strategy.

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

**REVISTA / JOURNAL:** - Cytotherapy. 2013 Oct 8. pii: S1465-3249(13)00633-6. doi: 10.1016/j.jcyt.2013.07.005.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.jcyt.2013.07.005](#)

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**RESUMEN / SUMMARY:** - BACKGROUND AIMS: Amniotic membrane (AM), the innermost layer of human placenta, is composed of a single layer of epithelial cells, a basement membrane and an avascular stroma. The AM has many functions and properties, among which angiogenic modulatory and immunoregulatory effects are applicable in cancer therapy. Because these functions belong to amniotic epithelial cells, in this study we compared the anti-cancer effect of amniotic epithelial cells and the whole AM. METHODS: The effect of the AM and the amniotic epithelial cells on cancer cell apoptosis was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium assay, terminal deoxynucleotidyl transferase dUTP nick end labeling assay and immunocytochemistry. The effect of the AM on angiogenesis in

conditions both with and without epithelial cells was also evaluated using rat aortic ring assay. RESULTS: There was a decrease in cancer cell viability after adding either AM or amniotic epithelial cell supernatant to cancer cells. A significant increase in caspase-3 and caspase-8 expression in cancer cells treated with amniotic epithelial cell supernatant was observed. The recorded media also demonstrated the possible induction of apoptosis in cancer cells treated with the amniotic epithelial cell supernatant. In the aorta ring assay, the AM showed an anti-angiogenic effect in the presence of its epithelial cells; however, this effect was altered to initiate angiogenesis when amniotic epithelial cells were removed from the AM. CONCLUSIONS: These results suggest that amniotic epithelial cells, with their anti-angiogenic effect and induction of apoptosis, are candidates for cancer therapeutic agents in the near future.

[154]

**TÍTULO / TITLE:** - Free somatostatin receptor fraction predicts the antiproliferative effect of octreotide in a neuroendocrine tumor model: implications for dose optimization.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Dec 1;73(23):6865-73. doi: 10.1158/0008-5472.CAN-13-1199. Epub 2013 Sep 30.

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

[1199](#)

**AUTORES / AUTHORS:** - Heidari P; Wehrenberg-Klee E; Habibollahi P; Yokell D; Kulke M; Mahmood U

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School and Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

**RESUMEN / SUMMARY:** - Somatostatin receptors (SSTR) are highly expressed in well-differentiated neuroendocrine tumors (NET). Octreotide, an SSTR agonist, has been used to suppress the production of vasoactive hormones and relieve symptoms of hormone hypersecretion with functional NETs. In a clinical trial, an empiric dose of octreotide treatment prolonged time to tumor progression in patients with small bowel neuroendocrine (carcinoid) tumors, irrespective of symptom status. However, there has yet to be a dose optimization study across the patient population, and methods are currently lacking to optimize dosing of octreotide therapy on an individual basis. Multiple factors such as total tumor burden, receptor expression levels, and nontarget organ metabolism/excretion may contribute to a variation in SSTR octreotide occupancy with a given dose among different patients. In this study, we report the development of an imaging method to measure surface SSTR expression and occupancy level using the PET radiotracer (68)Ga-DOTATOC. In an animal model, SSTR occupancy by octreotide was assessed quantitatively with (68)Ga-DOTATOC PET, with the finding that increased occupancy resulted in decreased tumor proliferation rate. The results suggested that quantitative SSTR imaging during octreotide therapy has the potential to determine the fractional receptor occupancy in NETs, thereby allowing octreotide dosing to be optimized readily in individual patients. Clinical trials validating this approach are warranted. Cancer Res; 73(23); 6865-73. ©2013 AACR.

[155]

**TÍTULO / TITLE:** - Application of gene expression programming and neural networks to predict adverse events of radical hysterectomy in cervical cancer patients.

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

**REVISTA / JOURNAL:** - Med Biol Eng Comput. 2013 Dec;51(12):1357-65. doi: 10.1007/s11517-013-1108-8. Epub 2013 Oct 18.

●● Enlace al texto completo (gratis o de pago) [1007/s11517-013-1108-8](#)

**AUTORES / AUTHORS:** - Kusy M; Obrzut B; Kluska J

**INSTITUCIÓN / INSTITUTION:** - Faculty of Electrical and Computer Engineering, Rzeszow University of Technology, W. Pola 2, 35-959, Rzeszow, Poland, [mkusy@prz.edu.pl](mailto:mkusy@prz.edu.pl).

**RESUMEN / SUMMARY:** - The aim of this article was to compare gene expression programming (GEP) method with three types of neural networks in the prediction of adverse events of radical hysterectomy in cervical cancer patients. One-hundred and seven patients treated by radical hysterectomy were analyzed. Each record representing a single patient consisted of 10 parameters. The occurrence and lack of perioperative complications imposed a two-class classification problem. In the simulations, GEP algorithm was compared to a multilayer perceptron (MLP), a radial basis function network neural, and a probabilistic neural network. The generalization ability of the models was assessed on the basis of their accuracy, the sensitivity, the specificity, and the area under the receiver operating characteristic curve (AUROC). The GEP classifier provided best results in the prediction of the adverse events with the accuracy of 71.96 %. Comparable but slightly worse outcomes were obtained using MLP, i.e., 71.87 %. For each of measured indices: accuracy, sensitivity, specificity, and the AUROC, the standard deviation was the smallest for the models generated by GEP classifier.

[156]

**TÍTULO / TITLE:** - Ponatinib: a new tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia.

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

**REVISTA / JOURNAL:** - Ann Pharmacother. 2013 Nov;47(11):1540-6. doi: 10.1177/1060028013501144. Epub 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1177/1060028013501144](#)

**AUTORES / AUTHORS:** - Shamroe CL; Comeau JM

**INSTITUCIÓN / INSTITUTION:** - Louisiana State University Health, Shreveport, LA, USA.

**RESUMEN / SUMMARY:** - OBJECTIVE: To review the pharmacology, pharmacokinetics, clinical trials, adverse effects, and formulary considerations of ponatinib, a pan-tyrosine kinase inhibitor (TKI). DATA SOURCES: A literature search of articles published between January 1966 and June 2013 was performed using PubMed with the following search terms: ponatinib, AP24534, and Iclusig. ARIAD Pharmaceuticals, Inc, was contacted for unpublished information. Other sources included American Society of Hematology abstracts, the Food and Drug Administration Center for Drug Evaluation and Research Web site, and clinicaltrials.gov. STUDY

SELECTION/DATA EXTRACTION: Included articles and abstracts were published in English and contain information about ponatinib, particularly in the treatment of chronic myeloid leukemia (CML) or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). DATA SYNTHESIS: Following the phase II PACE trial, ponatinib was approved for the treatment of patients with chronic-phase (CP), accelerated-phase (AP), or blast-phase (BP) CML or Ph+ ALL who have become intolerant or resistant to previous therapy. Unlike other BCR-ABL TKIs, ponatinib was designed to overcome the T315I mutation. At 15.3 months, 46% of patients with CP-CML achieved a complete cytogenetic response, and 34% achieved a major molecular response. Complete hematologic responses occurred in 47% of patients with AP-CML, 21% with BP-CML, and 34% with Ph+ ALL after 1 year. Severe toxicities included myelosuppression, hepatotoxicity, pancreatitis, and arterial thrombosis. CONCLUSIONS: Ponatinib is a potent TKI that can overcome several resistance mechanisms in previously treated patients with CML and Ph+ ALL. Ponatinib should be reserved for patients who have failed first-line therapy, have the T315I mutation, or have progressed.

[157]

**TÍTULO / TITLE:** - First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 21. doi: 10.1038/bjc.2013.721.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.721](#)

**AUTORES / AUTHORS:** - Douillard JY; Ostoros G; Cobo M; Ciuleanu T; McCormack R; Webster A; Milenkova T

**INSTITUCIÓN / INSTITUTION:** - Institut de Cancerologie de l'Ouest, Centre Rene Gauducheau, Bd J. Monod, 44805 St-Herblain, Nantes, France.

**RESUMEN / SUMMARY:** - Background:Phase-IV, open-label, single-arm study (NCT01203917) to assess efficacy and safety/tolerability of first-line gefitinib in Caucasian patients with stage IIIA/B/IV, epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC).Methods:Treatment: gefitinib 250 mg day-1 until progression. Primary endpoint: objective response rate (ORR). Secondary endpoints: disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety/tolerability. Pre-planned exploratory objective: EGFR mutation analysis in matched tumour and plasma samples.Results:Of 1060 screened patients with NSCLC (859 known mutation status; 118 positive, mutation frequency 14%), 106 with EGFR sensitising mutations were enrolled (female 70.8%; adenocarcinoma 97.2%; never-smoker 64.2%). At data cutoff: ORR 69.8% (95% confidence interval (CI) 60.5-77.7), DCR 90.6% (95% CI 83.5-94.8), median PFS 9.7 months (95% CI 8.5-11.0), median OS 19.2 months (95% CI 17.0-NC; 27% maturity). Most common adverse events (AEs; any grade): rash (44.9%), diarrhoea (30.8%); CTC (Common Toxicity Criteria) grade  $\geq$  3 AEs: 15%; SAEs: 19%. Baseline plasma 1 samples were available in 803 patients (784 known mutation status; 82 positive; mutation frequency 10%). Plasma 1 EGFR mutation test sensitivity: 65.7% (95% CI 55.8-74.7).Conclusion:First-line gefitinib was effective and well tolerated in Caucasian patients with EGFR mutation-positive NSCLC. Plasma samples could be considered

for mutation analysis if tumour tissue is unavailable. British Journal of Cancer advance online publication, 21 November 2013; doi:10.1038/bjc.2013.721 [www.bjcancer.com](http://www.bjcancer.com).

[158]

**TÍTULO / TITLE:** - Melanocortin 1 Receptor-derived peptides are efficiently recognized by cytotoxic T lymphocytes from melanoma patients.

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

**REVISTA / JOURNAL:** - Immunobiology. 2013 Oct 12. pii: S0171-2985(13)00177-0. doi: 10.1016/j.imbio.2013.10.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.imbio.2013.10.002](http://1016/j.imbio.2013.10.002)

**AUTORES / AUTHORS:** - Gonzalez FE; Ramirez M; Allerbring EB; Fasching N; Lundqvist A; Poschke I; Achour A; Salazar-Onfray F

**INSTITUCIÓN / INSTITUTION:** - Millennium Institute on Immunology and Immunotherapy, Faculty of Medicine, University of Chile, 8380453 Santiago, Chile; Science for Life Laboratory, Centre for Infectious Medicine (CIM), Department of Medicine, Karolinska University Hospital Huddinge, Karolinska Institute, Stockholm, Sweden; Department of Conservative Dentistry, Faculty of Dentistry, University of Chile, 8380492 Santiago, Chile.

**RESUMEN / SUMMARY:** - BACKGROUND: Melanocortin 1 Receptor (MC1R) is expressed in a majority of melanoma biopsies and cell lines. We previously demonstrated that three hydrophobic low-affinity HLA-A2-restricted MC1R-derived peptides: MC1R291-298, MC1R244-252 and MC1R283-291 can elicit cytotoxic T-lymphocytes (CTL) responses from normal donor peripheral blood lymphocytes (PBL). Moreover, peptide-specific CTL recognized a panel of MHC-matched melanomas, demonstrating that human melanoma cell lines naturally present MC1R epitopes. However, the natural presence of MC1R-specific T cells in melanoma patient's tumour and blood remains unknown. METHODS: The presence of anti-MC1R specific CD8+ T cells was established in a population of melanoma-specific T cells derived from peripheral blood mononuclear cells (PBMC) and tumour-infiltrating lymphocytes (TIL) from HLA-A2+ melanoma patients. RESULTS: CTLs specific for the three MC1R-derived peptides that lysed allogeneic HLA-A2+MC1R+ melanomas were elicited from PBMC, demonstrating the existence of an anti-MC1R T cell repertoire in melanoma patients. Moreover, TILs also recognized MC1R epitopes and HLA-A2+ melanoma cell lines. Finally, HLA-A2/MC1R244-specific CD8+ T cell clones derived from TILs and a subset of MC1R291 specific TILs were identified using HLA-A2/MC1R tetramers. CONCLUSION: Our results demonstrate that MC1R-derived peptides are common immunogenic epitopes for melanoma-specific CTLs and TILs, and may thus be useful for the development of anti-melanoma immunotherapy.

[159]

**TÍTULO / TITLE:** - Liver stiffness predicts hepatocellular carcinoma in chronic hepatitis C patients on interferon-based anti-viral therapy.

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

**REVISTA / JOURNAL:** - J Gastroenterol Hepatol. 2013 Oct 3. doi: 10.1111/jgh.12401.

●● Enlace al texto completo (gratis o de pago) [1111/jgh.12401](http://1111/jgh.12401)

**AUTORES / AUTHORS:** - Narita Y; Genda T; Tsuzura H; Sato S; Kanemitsu Y; Ishikawa S; Kikuchi T; Hirano K; Iijima K; Wada R; Ichida T

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, Shizuoka, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND AND AIM: The purpose of this study was to evaluate the usefulness of liver stiffness measurement (LSM) for assessing the risk of hepatocellular carcinoma (HCC) in chronic hepatitis C (CHC) patients receiving interferon (IFN) therapy. METHODS: One hundred fifty-one CHC patients who underwent LSM and received IFN therapy were included in the estimation cohort, and 56 were included in the validation study. The cumulative HCC incidences were evaluated using Kaplan-Meier plot analysis and the log-rank test. Multivariate Cox proportional hazard analyses were used to estimate the hazard ratios (HRs) of variables for HCC. RESULTS: In the estimation cohort, 9 of 151 patients developed HCC during the median follow-up time of 722 days. Multivariate analysis identified 3 independent risk factors for HCC: LSM ( $\geq 14.0$  kPa, HR 5.58,  $P = 0.020$ ), platelet count ( $< 14.1 \times 10^4/\mu\text{L}$ , HR 5.59,  $P = 0.034$ ), and non-sustained virological response (HR 8.28,  $P = 0.049$ ). The cumulative incidence of HCC development at 3 years was 59.6%, 8.2%, and 0.0% in patients with all 3 risk factors, 1-2 risk factors, and none of these risk factors, respectively. The incidence of HCC was significantly different between these groups ( $P < 0.001$ ). In the validation cohort, HCC incidence was also significantly different with respect to these risk factors ( $P = 0.037$ ). CONCLUSION: LSM, platelet count, and IFN-therapeutic effect could be used to successfully stratify the risk of HCC in patients receiving IFN therapy and demonstrate the usefulness of LSM before IFN therapy for the management of CHC patients.

[160]

**TÍTULO / TITLE:** - Cyclin E1 (CCNE1) as independent positive prognostic factor in advanced stage serous ovarian cancer patients - A study of the OVCAD consortium.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Oct 28. pii: S0959-8049(13)00851-4. doi: 10.1016/j.ejca.2013.09.011.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ejca.2013.09.011](#)

**AUTORES / AUTHORS:** - Pils D; Bachmayr-Heyda A; Auer K; Svoboda M; Auner V; Hager G; Obermayr E; Reiner A; Reinhaller A; Speiser P; Braicu I; Sehoul J; Lambrechts S; Vergote I; Mahner S; Berger A; Cacsire Castillo-Tong D; Zeillinger R

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Molecular Oncology Group, Medical University of Vienna, Vienna, Austria. Electronic address: [dietmar.pils@univie.ac.at](mailto:dietmar.pils@univie.ac.at).

**RESUMEN / SUMMARY:** - Cyclin E, coded by the genes CCNE1 and CCNE2, is the main regulator for transition from G1 to S phase determining cell division. CCNE1 and CCNE2 are known oncogenes in many cancer entities. Especially CCNE1 has frequently been associated with gene amplifications in various malignancies, emphasising its role as a putative oncogene. We determined gene expression and copy number of CCNE1 and CCNE2 by quantitative polymerase chain reaction (PCR) from 172 International Federation of Obstetrics and Gynecology (FIGO) II/III/IV stage serous epithelial ovarian cancer (EOC) tissues and analysed its impact on outcome. Furthermore, whole transcriptome gene expression changes correlating with CCNE1

expression were determined by microarray technology, interpreted by Signalling Pathway Impact Analysis (SPIA), Tool for Inferring Network of Genes (TINGe), and illustrated by hive plots. Protein-protein interaction (PPI) networks were also used for the interpretation. Interestingly, and contradictory to most reports and intuitive expectations, high CCNE1 expression correlated with better overall survival ( $p=0.005$ ) if corrected for usual clinicopathologic parameters and a molecular subclassification. Using different grading systems or only high graded tumours had no impact on this correlation. Copy number of CCNE1 was increased in 25% of cases which correlated highly significantly with expression but showed no impact on outcome. CCNE2 had no impact on outcomes at all. Whole genome transcriptome analysis revealed 1872 differentially expressed genes correlated to CCNE1 expression, which were significantly enriched with genes from five pathways (e.g. cell cycle and viral carcinogenesis pathway were up-regulated and the Fanconi anaemia pathway was down-regulated). High CCNE1 gene expression is a significant and independent predictor for prolonged overall survival in FIGO III/IV EOC patients. This upside down impact of CCNE1 on survival probably reflects the special characteristic of EOC with tumour dissemination in the near anaerobic peritoneal cavity as the predominant cause of death, compared to other cancer entities where distant metastasis are predominantly lethal.

[161]

**TÍTULO / TITLE:** - A novel discriminant score based on tumor-associated trypsin inhibitor for accurate diagnosis of metastasis in patients with breast cancer.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1366-y](#)

**AUTORES / AUTHORS:** - El-Mezayen HA; Metwally FM; Darwish H

**INSTITUCIÓN / INSTITUTION:** - Chemistry Department, Helwan University, Cairo, Egypt, [hatem\\_mezayen@yahoo.com](mailto:hatem_mezayen@yahoo.com).

**RESUMEN / SUMMARY:** - Invasion and metastasis of solid tumors require proteolytic enzymes for degradation of the basal membrane and extracellular matrix. Currently, there are no reliable methodologies to predict the risk for metastatic disease. In this context, our aim has been focused on the development of a noninvasive score based on tumor-associated trypsin inhibitor (TATI) for the assessment of metastasis in patients with breast cancer. TATI, trypsin, and soluble epidermal growth factor receptor (sEGFR) were assayed by enzyme-linked immunosorbent assay. CA 15.3 serum level was assayed by microparticle enzyme immunoassay in 265 patients with breast cancer. Statistical analyses were performed by logistic regression and receiver operating characteristic analysis curves. Using multivariate discriminant analysis, a score is selected based on absolute values of the four biochemical markers: TATI-metastatic breast cancer score (TATI-MBCS) =  $[0.03 \times \text{CA 15.3 (U/L)} + 0.039 \times \text{TATI (ng/ml)} + 0.04 \times \text{trypsin (ng/ml)} + 0.023 \times \text{sEGFR (ng/ml)} - 6.49 \text{ (numerical constant)}]$ . This function correctly classified 84 % of metastatic breast cancer at cutoff value = 0.62 (i.e., greater than 0.62 indicates patients with metastatic breast cancer and less than 0.62 indicates patients with nonmetastatic breast cancer). In conclusion, TATI-MBCS is a novel, noninvasive, and simple score which can be applied to discriminate patients with metastatic breast cancer.

[162]

**TÍTULO / TITLE:** - In silico calculated affinity of FVIII-derived peptides for HLA class II alleles predicts inhibitor development in haemophilia A patients with missense mutations in the F8 gene.

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

**REVISTA / JOURNAL:** - Haemophilia. 2013 Oct 14. doi: 10.1111/hae.12276.

●● [Enlace al texto completo \(gratis o de pago\) 1111/hae.12276](#)

**AUTORES / AUTHORS:** - Pashov AD; Calvez T; Gilardin L; Maillere B; Repesse Y; Oldenburg J; Pavlova A; Kaveri SV; Lacroix-Desmazes S

**INSTITUCIÓN / INSTITUTION:** - Centre de recherche des Cordeliers, INSERM, UMR S 872, Paris, France; Centre de Recherche des Cordeliers, Université Pierre et Marie Curie-Paris6, UMR S 872, Paris, France; Centre de Recherche des Cordeliers, Université Paris Descartes, UMR S 872, Paris, France; Department of Immunology, Institute of Microbiology, BAS, Sofia, Bulgaria.

**RESUMEN / SUMMARY:** - Forty per cent of haemophilia A (HA) patients have missense mutations in the F8 gene. Yet, all patients with identical mutations are not at the same risk of developing factor VIII (FVIII) inhibitors. In severe HA patients, human leucocyte antigen (HLA) haplotype was identified as a risk factor for onset of FVIII inhibitors. We hypothesized that missense mutations in endogenous FVIII alter the affinity of the mutated peptides for HLA class II, thus skewing FVIII-specific T-cell tolerance and increasing the risk that the corresponding wild-type FVIII-derived peptides induce an anti-FVIII immune response during replacement therapy. Here, we investigated whether affinity for HLA class II of wild-type FVIII-derived peptides that correspond to missense mutations described in the Haemophilia A Mutation, Structure, Test and Resource database is associated with inhibitor development. We predicted the mean affinity for 10 major HLA class II alleles of wild-type FVIII-derived peptides that corresponded to 1456 reported cases of missense mutations. Linear regression analysis confirmed a significant association between the predicted mean peptide affinity and the mutation inhibitory status ( $P = 0.006$ ). Significance was lost after adjustment on mutation position on FVIII domains. Although analysis of the A1-A2-A3-C1 domains yielded a positive correlation between predicted HLA-binding affinity and inhibitory status (OR = 0.29 [95% CI: 0.14-0.60] for the high affinity tertile,  $P = 0.002$ ), the C2 domain-restricted analysis indicated an inverse correlation (OR = 3.56 [1.10-11.52],  $P = 0.03$ ). Our data validate the importance of the affinity of FVIII peptides for HLA alleles to the immunogenicity of therapeutic FVIII in patients with missense mutations.

[163]

**TÍTULO / TITLE:** - MicroRNAs, miR-154, miR-299-5p, miR-376a, miR-376c, miR-377, miR-381, miR-487b, miR-485-3p, miR-495 and miR-654-3p, mapped to the 14q32.31 locus, regulate proliferation, apoptosis, migration and invasion in metastatic prostate cancer cells.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Oct 28. doi: 10.1038/onc.2013.451.

●● [Enlace al texto completo \(gratis o de pago\) 1038/onc.2013.451](#)

**AUTORES / AUTHORS:** - Formosa A; Markert EK; Lena AM; Italiano D; Finazzi-Agro' E; Levine AJ; Bernardini S; Garabadgiu AV; Melino G; Candi E

**INSTITUCIÓN / INSTITUTION:** - 1] University of Tor Vergata, Department Experimental Medicine and Surgery, Rome, Italy [2] IDI-IRCCS, Rome, Italy.

**RESUMEN / SUMMARY:** - miRNAs act as oncogenes or tumor suppressors in a wide variety of human cancers, including prostate cancer (PCa). We found a severe and consistent downregulation of miRNAs, miR-154, miR-299-5p, miR-376a, miR-376c, miR-377, miR-381, miR-487b, miR-485-3p, miR-495 and miR-654-3p, mapped to the 14q32.31 region in metastatic cell lines as compared with normal prostatic epithelial cells (PrEC). In specimens of human prostate (28 normals, 99 primary tumors and 13 metastases), lower miRNA levels correlated significantly with a higher incidence of metastatic events and higher prostate specific antigen (PSA) levels, with similar trends observed for lymph node invasion and the Gleason score. We transiently transfected 10 members of the 14q32.31 cluster in normal prostatic epithelial cell lines and characterized their affect on malignant cell behaviors, including proliferation, apoptosis, migration and invasion. Finally, we identified FZD4, a gene important for epithelial-to-mesenchymal transition in (PCa), as a target of miR-377. Oncogene advance online publication, 28 October 2013; doi:10.1038/onc.2013.451.

[164]

**TÍTULO / TITLE:** - Serum lemur tyrosine kinase 3 expression in colorectal cancer patients predicts cancer progression and prognosis.

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

**REVISTA / JOURNAL:** - Med Oncol. 2013 Dec;30(4):754. doi: 10.1007/s12032-013-0754-x. Epub 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0754-x](#)

**AUTORES / AUTHORS:** - Shi H; Wu J; Ji M; Zhou Q; Li Z; Zheng X; Xu B; Deng H; Zhao W; Wu C; Jiang J

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou, 213003, Jiangsu Province, China.

**RESUMEN / SUMMARY:** - Lemur tyrosine kinase-3 (LMTK3) is a member of the families of serine-threonine-tyrosine kinases, which has been suggested to be a possible target and marker of breast cancer. However, its definitive physiopathological function in colorectal cancer (CRC) is poorly understood at present. The aim of this study was to determine the expression levels of preoperative-soluble LMTK3 (sLMTK3) in patients' blood with CRC and to subsequently evaluate whether or not its level in serum can be used to predict cancer progression and prognosis. The expression levels of sLMTK3 were measured by sandwich enzyme-linked immunosorbent assay in blood specimens from 60 patients with CRC and 53 healthy volunteers. As a result, we found that the mean concentration of sLMTK3 in CRC patients was significantly higher than that in healthy volunteers ( $P = 0.012$ ). The expression levels of sLMTK3 were significantly correlated with histological subtype, depth of tumor invasion, and tumor-node-metastasis (TNM) classification ( $P = 0.038$ ,  $0.021$ , and  $0.049$ , respectively), but not with sex, age, tumor location, tumor size, or lymph node metastasis. Additionally, Kaplan-Meier survival curves showed that patients with high levels of sLMTK3 had a poorer overall survival rate when compared with those of patients with low levels of sLMTK3 ( $P = 0.041$ ). Moreover, multivariate analysis demonstrated that sLMTK3

expression and TNM stage were independent prognostic factors for CRC patients ( $P = 0.047$  and  $0.008$ , respectively). These results suggest that serum LMTK3 could be a valuable biomarker for predicting the progression and prognosis of patients with CRC.

[165]

**TÍTULO / TITLE:** - TNK2 gene amplification is a novel predictor of a poor prognosis in patients with gastric cancer.

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

**REVISTA / JOURNAL:** - J Surg Oncol. 2013 Oct 31. doi: 10.1002/jso.23482.

●● Enlace al texto completo (gratis o de pago) [1002/jso.23482](#)

**AUTORES / AUTHORS:** - Shinmura K; Kiyose S; Nagura K; Igarashi H; Inoue Y; Nakamura S; Maeda M; Baba M; Konno H; Sugimura H

**INSTITUCIÓN / INSTITUTION:** - Department of Tumor Pathology, Hamamatsu University School of Medicine, Hamamatsu, Japan.

**RESUMEN / SUMMARY:** - **BACKGROUND AND OBJECTIVES:** We previously examined the amplification status of 10 kinase genes (PIK3CA, EPHB3, TNK2, PTK7, EGFR, MET, ERBB2, HCK, SRC, and AURKA) in gastric cancer (GC). This study aimed to determine the prognostic significance of these gene amplifications in GC. **METHODS:** A survival analysis was performed for GC patients. Since TNK2 amplification was identified as a prognostic marker in the analysis, we also examined the functional effect of TNK2 overexpression on gastric cells. **RESULTS:** A Kaplan-Meier analysis showed that the prognosis of patients with GC exhibiting TNK2 or AURKA amplification was significantly poorer than the prognosis of patients with GC without TNK2 or AURKA amplification. A further multivariate analysis revealed that TNK2 amplification was an independent predictor of a poor survival outcome among patients with GC (hazard ratio, 3.668; 95% confidence interval, 1.513-7.968;  $P = 0.0056$ ). TNK2-overexpressing GC cells showed an increase in cell migration and non-anchored cell growth. Finally, microarray and pathway analyses revealed the aberrant regulation of some cancer-related pathways in TNK2-overexpressing GC cells. **CONCLUSIONS:** These results suggested that TNK2 amplification is an independent predictor of a poor prognosis in patients with GC and leads to an increase in the malignant potential of GC cells. J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

[166]

**TÍTULO / TITLE:** - Activated Cdc42-associated Kinase 1 (Ack1) Is Required for Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL) Receptor Recruitment to Lipid Rafts and Induction of Cell Death.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 15;288(46):32922-31. doi: 10.1074/jbc.M113.481507. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.481507](#)

**AUTORES / AUTHORS:** - Linderoth E; Pilia G; Mahajan NP; Ferby I

**INSTITUCIÓN / INSTITUTION:** - From the Wolfson Institute for Biomedical Research, University College London, WC1E 6BT London, United Kingdom.

**RESUMEN / SUMMARY:** - TNF-related apoptosis-inducing ligand (TRAIL) holds promise for treatment of cancer due to its ability to selectively kill cancer cells while sparing

normal cells. Ligand-induced translocation of TRAIL receptors (TRAIL-R) 1 and 2 (also called DR4 and DR5, respectively) into lipid raft membrane microdomains is required for TRAIL-induced cell death by facilitating receptor clustering and formation of the death-inducing signaling complex, yet the underlying regulatory mechanisms remain largely unknown. We show here that the non-receptor tyrosine kinase Ack1, previously implicated in the spatiotemporal regulation of the EGF receptor, is required for TRAIL-induced cell death in multiple epithelial cell lines. TRAIL triggered a transient up-regulation of Ack1 and its recruitment to lipid rafts along with TRAIL-R1/2. siRNA-mediated depletion of Ack1 disrupted TRAIL-induced accumulation of TRAIL-R1/2 in lipid rafts and efficient recruitment of caspase-8 to the death-inducing signaling complex. Pharmacological inhibition of Ack1 did not affect TRAIL-induced cell death, indicating that Ack1 acts in a kinase-independent manner to promote TRAIL-R1/2 accumulation in lipid rafts. These findings identify Ack1 as an essential player in the spatial regulation of TRAIL-R1/2.

[167]

**TÍTULO / TITLE:** - CD20 Antigen May Be Expressed by Reactive or Lymphomatous Cells of Transformed Mycosis Fungoides: Diagnostic and Prognostic Impact.

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

**REVISTA / JOURNAL:** - Am J Surg Pathol. 2013 Dec;37(12):1845-54. doi: 10.1097/PAS.0000000000000091.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1097/PAS.0000000000000091](#)

**AUTORES / AUTHORS:** - Jullie ML; Carlotti M; Vivot A Jr; Beylot-Barry M; Ortonne N; Frouin E; Carlotti A; de Muret A; Balme B; Franck F; Merlio JP; Vergier B

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**RESUMEN / SUMMARY:** - Mycosis fungoides (MF), the most common primitive cutaneous T-cell lymphoma, can undergo transformation in about 10% of cases. Transformed mycosis fungoides (T-MF) is often associated with the appearance of a CD20 component. The aim of this study was to analyze whether such cells are reactive or lymphomatous and to evaluate their prognostic impact. Among 311 T-MFs from the French Cutaneous Lymphoma Study Group registry, we studied 148 cases. CD20 was expressed in 88 cases (59%). The proportion of CD20 cells among T-MF lesions was <10% for 54 cases (38%), 10% to 49% for 71 cases (81%), and >50% for 17 cases (19%). We focused the study on 23 cases that contained >50% CD20 cells. To evaluate the nature of the CD20 component, we used immunohistochemistry (2 anti-CD20 antibodies, L26 and 7D1 clones, and 2 other anti-B-cell antigen antibodies, CD22 and PAX5) and a double-stain immunofluorescence technique (anti-CD20 and anti-CD3 antibodies). The clonality of B cells was studied by polymerase chain

reaction. Three profiles were observed. In 15 of the 23 cases, the CD20 cells were reactive. In 6 cases, CD20 protein was aberrantly expressed in T-MF lesions. Lastly, there were 2 composite lymphomas (T-MF infiltrate with a B-cell follicular lymphoma). In view of this series, we propose a simple algorithm to help pathologists evaluate the nature of the CD20 component associated with T-MF. Although statistically not significant, there was a trend toward a worse prognosis in the presence of >50% CD20 cells and of a nodular perifollicular pattern of this component.

[168]

**TÍTULO / TITLE:** - Cancerous inhibitor of protein phosphatase 2A (CIP2A) is involved in centrosome separation through the regulation of NIMA-related kinase 2 (NEK2) activity.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 8.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.507954](http://1074/jbc.M113.507954)

**AUTORES / AUTHORS:** - Jeong AL; Lee S; Park JS; Han S; Jang CY; Lim JS; Lee MS; Yang Y

**INSTITUCIÓN / INSTITUTION:** - Sookmyung Women's University, Korea, Republic of.

**RESUMEN / SUMMARY:** - Cancerous inhibitor of protein phosphatase 2A (CIP2A) is overexpressed in most human cancers and has been described as being involved in the progression of several human malignancies via the inhibition of protein phosphatase 2A (PP2A) activity toward c-Myc. However, with the exception of this role, the cellular function of CIP2A remains poorly understood. Based on yeast two-hybrid and co-immunoprecipitation assays, we demonstrate here that NIMA-related kinase 2 (NEK2) is a binding partner for CIP2A. CIP2A exhibited dynamic changes in distribution, including the cytoplasm and centrosome, depending on the cell cycle stage. When CIP2A was depleted, centrosome separation and the mitotic spindle dynamics were impaired, resulting in the activation of SAC signaling and, ultimately, extension of the cell division time. Our data imply that CIP2A strongly interacts with NEK2 during the G2 phase, thereby enhancing NEK2 kinase activity to facilitate centrosome separation in a PP1 and PP2A-independent manner. In conclusion, CIP2A is involved in cell cycle progression through centrosome separation and mitotic spindle dynamics.

[169]

**TÍTULO / TITLE:** - BAP1 protein loss by immunohistochemistry: a potentially useful tool for prognostic prediction in patients with uveal melanoma.

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

**REVISTA / JOURNAL:** - Pathology. 2013 Dec;45(7):651-6. doi: 10.1097/PAT.0000000000000002.

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

[1097/PAT.0000000000000002](http://1097/PAT.0000000000000002)

**AUTORES / AUTHORS:** - Shah AA; Bourne TD; Murali R

**INSTITUCIÓN / INSTITUTION:** - \*Department of Pathology, University of Virginia School of Medicine, Charlottesville VA daggerDepartment of Pathology double daggerHuman Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY, United States.

**RESUMEN / SUMMARY:** - BACKGROUND: Uveal melanoma is the most common primary malignant intraocular tumour in adults. Recently, biallelic inactivation of the BAP1 gene was shown to be associated with increased risk of metastasis in patients with uveal melanoma. Immunohistochemical (IHC) assessment of BAP1 protein loss has been shown to be an excellent surrogate for biallelic inactivation of BAP1. In this pilot study, we investigated whether loss of BAP1 expression by IHC is associated with prognosis in uveal melanoma patients. METHODS: We retrieved clinical data, reviewed pathological slides, and performed IHC for BAP1 in 40 primary uveal melanomas. Tumour cell type was classified as: spindle (>90% spindle cells); epithelioid (>90% epithelioid cells); or mixed. BAP1 expression was scored as diffuse (nuclear staining in >90% of tumour cells), heterogenous (nuclear staining in <90% of tumour cells), or absent (no nuclear staining). We analysed associations of BAP1 expression with clinical and pathological parameters, and with overall survival. RESULTS: Tumours were obtained from 20 males and 20 females, with a median age of 60 years (range 31-81 years). Tumour cell types were: epithelioid (n = 7, 18%), mixed (n = 20, 50%), and spindled (n = 13, 33%). BAP1 expression was absent in 23 (58%) tumours, heterogenous in seven (18%) tumours, and diffuse in 10 (25%) tumours. Absent BAP1 expression was more frequently seen in epithelioid/mixed cell tumours (19/27, 70%) than was heterogenous (3/27, 11%) or diffuse (5/27, 19%) expression; the corresponding figures for spindle cell tumours were 4/13 (31%), 4/13 (31%) and 5/13 (38%), respectively (p = 0.057). Factors associated with improved survival were diffuse or heterogenous BAP1 expression (compared with absent expression, p = 0.03) and age less than 60 years (p = 0.049). CONCLUSION: Analysis of BAP1 protein expression using immunohistochemistry may serve as a rapid and cost-effective means of identifying uveal melanoma patients with aggressive disease, who can then be managed appropriately.

[170]

**TÍTULO / TITLE:** - microRNA expression profiles associated with survival, disease progression, and response to gefitinib in completely resected non-small-cell lung cancer with EGFR mutation.

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

**REVISTA / JOURNAL:** - Med Oncol. 2013 Dec;30(4):750. doi: 10.1007/s12032-013-0750-1. Epub 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0750-1](#)

**AUTORES / AUTHORS:** - Shen Y; Tang D; Yao R; Wang M; Wang Y; Yao Y; Li X; Zhang H

**INSTITUCIÓN / INSTITUTION:** - Medical College, Thoracic Surgery of the Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao, 266003, China.

**RESUMEN / SUMMARY:** - microRNAs have been implicated in regulating diverse cellular pathways. Although there is emerging evidence that some microRNAs can function as oncogenes or tumor suppressors, the role of microRNAs in mediating cancer progression remains unexplored. And whether expression levels of a panel of biologically relevant microRNAs can be used as prognostic or predictive biomarkers in radically resected non-small-cell lung carcinoma (NSCLC) patients still needs to be further validated. Our analyses involved two separated, retrospective cohorts. Firstly, microRNA expression profile was performed in a cohort consisted of 128 radically

resected NSCLC patients [60 were positive to epidermal growth factor receptor (EGFR) mutation and 68 were negative] and 32 healthy providers to identify EGFR mutation-related microRNAs and to determine their association with survival. In addition, to validate our findings, we used quantitative reverse transcriptase polymerase chain reaction assays to measure microRNAs and assess their association with disease progression, survival, and response to gefitinib in an independent cohort of 201 patients with EGRF mutation. In radically resected NSCLC patients, the expression levels of miR-21, 10b in patients with EGFR mutation were much higher than those without mutation. We used Cox proportional-hazards regression to evaluate the effect of treatment on survival. In both univariate and multivariate analyses, gefitinib was associated with a significant improvement in overall survival in patients with reduced miR-21 expression. Thus, miR-21 expression emerged as an independent predictor of the response to gefitinib. Additionally, miR-10b is highly expressed in progressive disease compared with complete remission or stable disease ( $P < 0.001$ ). However, miR-21 expression has no significant prognosis for disease progression ( $P = 0.720$ ). Meanwhile, when overall survival was considered as the end point, miR-10b did not have a significant difference between different subgroups ( $P = 0.634$ ). The expression patterns of microRNAs differ significantly between patients with positive and negative EGFR mutation. And the expression status of miR-21 and 10b in such patients is associated with disease progression, survival, and response to adjuvant therapy with gefitinib.

[171]

**TÍTULO / TITLE:** - Characterization of SNARE Proteins in Human Pituitary Adenomas: Targeted Secretion Inhibitors as a New Strategy for the Treatment of Acromegaly?

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

**REVISTA / JOURNAL:** - J Clin Endocrinol Metab. 2013 Oct 23.

●● Enlace al texto completo (gratis o de pago) [1210/jc.2013-2602](#)

**AUTORES / AUTHORS:** - Garcia EA; Trivellin G; Aflorci ED; Powell M; Grieve J; Alusi G; Pobereskin L; Shariati B; Cudlip S; Roncaroli F; Mendoza N; Grossman AB; Harper EA; Korbonits M

**INSTITUCIÓN / INSTITUTION:** - Centre for Endocrinology (E.A.G., G.T., E.D.A., A.B.G., M.K.), William Harvey Research Institute, Department of Neurosurgery (I.S.) and Barts Cancer Institute (G.A.), Barts, and The London School of Medicine, London, United Kingdom; The National Hospital for Neurology and Neurosurgery (M.P., J.G.), University College London, London, United Kingdom; Department of Neurosurgery (L.P.), Derriford Hospital, Derriford, United Kingdom; Division of Brain Sciences (B.S., F.R., NM), "John Fulcher" Laboratory, Imperial College, London, United Kingdom; Department of Neurosurgery (S.C.), John Radcliffe Hospital, Oxford, United Kingdom; Oxford Centre for Diabetes (A.B.G.), Endocrinology, and Metabolism, University of Oxford, Oxford, United Kingdom; and Syntaxin Ltd (E.A.H.), Abingdon, United Kingdom.

**RESUMEN / SUMMARY:** - Context: Targeted secretion inhibitors (TSIs), a new class of recombinant biotherapeutic proteins engineered from botulinum toxin, represent a novel approach for treating diseases with excess secretion. They inhibit hormone secretion from targeted cell types through cleavage of SNARE (soluble N-ethylmaleimide-sensitive factor-activating protein receptor) proteins. qGHRH-LHN/D is

a TSI targeting pituitary somatotroph through binding to the GHRH-receptor and cleavage of the vesicle-associated membrane protein (VAMP) family of SNARE proteins. Objective: To study SNARE protein expression in pituitary adenomas and to inhibit GH secretion from somatotropinomas using qGHRH-LHN/D. Design: Human pituitary adenoma analysis for SNARE expression and response to qGHRH-LHN/D treatment. Setting: University hospital. Patients: Twenty-five acromegaly and 47 nonfunctioning pituitary adenoma patients. Outcome: Vesicle-SNARE (VAMP1-3), target-SNARE (syntaxin1, SNAP-23, and SNAP-25), and GHRH-R detection with RT-qPCR, immunocytochemistry, and immunoblotting. Assessment of TSI catalytic activity on VAMPs and release of GH from adenoma cells. Results: SNARE proteins were variably expressed in pituitary samples. In vitro evidence using recombinant GFP-VAMP2&3 or pituitary adenoma lysates suggested sufficient catalytic activity of qGHRH-LHN/D to degrade VAMPs, but was unable to inhibit GH secretion in somatotropinoma cell cultures. Conclusions: SNARE proteins are present in human pituitary somatotroph adenomas that can be targeted by TSIs to inhibit GH secretion. qGHRH-LHN/D was unable to inhibit GH secretion from human somatotroph adenoma cells. Further studies are required to understand how the SNARE proteins drive GH secretion in human somatotrophs to allow the development of novel TSIs with a potential therapeutic benefit.

[172]

**TÍTULO / TITLE:** - Nutritional Status Is Superior to the ECOG Performance Status in Predicting the Dose-Intensity of the GEMOX Chemotherapy Regimen in Patients with Advanced Cancer.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65(8):1254-7. doi: 10.1080/01635581.2013.830315. Epub 2013 Oct 7.

•• [Enlace al texto completo \(gratis o de pago\) 1080/01635581.2013.830315](#)

**AUTORES / AUTHORS:** - Cessot A; Coriat R; Mir O; Boudou-Rouquette P; Giroux J; Durand JP; Alexandre J; Goldwasser F

**INSTITUCIÓN / INSTITUTION:** - a Department of Medical Oncology, Cochin Teaching Hospital, Assistance Publique-Hopitaux de Paris, Paris Descartes University, France.

**RESUMEN / SUMMARY:** - The increasing number of unfit patients calls for better risk assessment prior to initiating anti-tumor treatment. This is a major concern in the prevention and reduction of treatment-related complications. The aim of our study was to evaluate the nutritional status for the risk assessment of patients qualifying to receive the gemcitabine and oxaliplatin (GEMOX) regimen. This single-center, retrospective study examined baseline clinical and biological characteristics in a cohort of 165 unselected, consecutive cancer patients receiving GEMOX. Malnutrition was defined as either body mass index (BMI) <18.5 kg/m<sup>2</sup>, body weight loss >10% over 3 mo, or albuminemia <35 g/L. A total of 165 patients (median age 61 yr, PS 0-1: 71%) were studied. Malnutrition was seen in 43% of PS 0-1 patients, vs. 60% of PS 2 and 66% of PS 3 patients (P > 0.05). Median relative dose-intensity was 0.90 (0.17-1.04). GEMOX dose-intensity correlated negatively with loss of baseline weight (r = -0.24, P < 0.02). In patients who did not complete more than 2 cycles of chemotherapy, median PS (P < 0.01), mean C-reactive protein (CRP; P < 0.01), and mean albuminemia (P < 0.05) were, respectively, significantly higher, higher, and lower. Malnutrition is

associated with a high risk of early discontinuance of treatment. Systematic basal evaluation of the nutritional status, including albuminemia and BMI, is recommended.

[173]

**TÍTULO / TITLE:** - ATM and TGFB1 genes polymorphisms in prediction of late complications of chemoradiotherapy in patients with locally advanced cervical cancer.

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

**REVISTA / JOURNAL:** - Neoplasma. 2014;61(1):70-6.

**AUTORES / AUTHORS:** - Paulikova S; Petera J; Sirak I; Vosmik M; Drastikova M; Dusek L; Cvanova M; Soumarova R; Spacek J; Beranek M

**RESUMEN / SUMMARY:** - The purpose of our study was to evaluate a possible correlation between genetic polymorphisms in ATM and TGFB1 genes and late toxicity of chemoradiotherapy for locally advanced cervical cancer. Fifty five patients with FIGO stage IIB and higher without adisease recurrence with a mean follow up of 6 years were included. Late toxicity was assessed by EORTC/RTOG late toxicity criteria. Univariate and multivariate logistic regression model was used for statistical analysis. Degree of association between polymorphisms and late toxicity of chemotherapy was assessed on the basis of phi-coefficient (phi) as well. We did not find any association between 5557G>A polymorphism in the ATM gene or single TGFB1 polymorphisms and late toxicity. TGFB1 compound homozygosity (-1552delAGG, -509C>T, L10P) was a significant predictive factor of grade III-IV and any grade of complications in both univariate and multivariate logistic regression analyses and statistical significance of association between polymorphisms and late toxicity of chemoradiotherapy was confirmed also by the evaluation of phi-coefficient (phi). We conclude that haplotypes instead of single nucleotide polymorphic sites in the genes may better characterize the individual radiosensitivity. Keywords: cervical cancer, radiotherapy, ATM, TGFB1, late toxicity.

[174]

**TÍTULO / TITLE:** - Expression of fibroblast growth factor 9 is associated with poor prognosis in patients with resected non-small cell lung cancer.

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

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Oct 30. pii: S0169-5002(13)00460-1. doi: 10.1016/j.lungcan.2013.10.016.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.lungcan.2013.10.016](#)

**AUTORES / AUTHORS:** - Ohgino K; Soejima K; Yasuda H; Hayashi Y; Hamamoto J; Naoki K; Arai D; Ishioka K; Sato T; Terai H; Ikemura S; Yoda S; Tani T; Kuroda A; Betsuyaku T

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

**RESUMEN / SUMMARY:** - OBJECTIVES: Fibroblast growth factor (FGF) 9 is a member of the FGF family, which modulates cell proliferation, differentiation, and motility. Recent studies show that the activation of FGF signals including FGF9 is associated with the pathogenesis of several cancers; however, its clinicopathological and biological significance in non-small cell lung cancer (NSCLC) is unclear. The purpose of this study was to clarify the characteristics of NSCLC with FGF9 expression.

**MATERIALS AND METHODS:** We evaluated the expression of FGF9 in resected NSCLC specimens and corresponding non-tumorous lung tissue samples using cDNA microarray and evaluated its clinicopathological characteristics. **RESULTS:** Nine out of 90 NSCLC specimens (10%) had “high” FGF9 expression compared with corresponding non-cancerous lung tissues. Histologically, of the 9 NSCLC specimens with high FGF9 expression, 5 were adenocarcinoma, whereas none were squamous cell carcinoma. FGF9 expression was not associated with sex, smoking history, or clinical stage. However, in patients with high and low FGF9 expression, the postoperative recurrence rates were 78% and 24% ( $p=0.033$ ), respectively. Overall survival was significantly shorter in patients with high FGF9 expression than in those with low FGF9 expression ( $p<0.001$ ). **CONCLUSION:** Our data indicate that FGF9 may be a novel unfavorable prognostic indicator and a candidate therapeutic target of NSCLC.

[175]

**TÍTULO / TITLE:** - Advanced Lung Adenocarcinoma Harboring a Mutation of the Epidermal Growth Factor Receptor: CT Findings after Tyrosine Kinase Inhibitor Therapy.

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

**REVISTA / JOURNAL:** - Radiology. 2013 Oct 1.

●● [Enlace al texto completo \(gratis o de pago\) 1148/radiol.13121824](#)

**AUTORES / AUTHORS:** - Choi CM; Kim MY; Lee JC; Kim HJ

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary and Critical Care Medicine, Department of Oncology, Department of Radiology and Research Institute of Radiology, and Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul 138-736, Korea.

**RESUMEN / SUMMARY:** - Purpose: To study chest computed tomography (CT) in tyrosine kinase inhibitor (TKI) treatment of epidermal growth factor receptor (EGFR)-mutant adenocarcinoma. Materials and Methods: This retrospective study was approved by the institutional review board. Informed consent was waived. One hundred thirty consecutive patients with stage IV adenocarcinoma and EGFR mutations at a single tertiary center from November 2004 to April 2010 were enrolled retrospectively. CT images were analyzed with Response Evaluation Criteria in Solid Tumor guidelines. Target lesions were classified by size, type, axial location, and metastasis. Patients were followed after TKI therapy, and treatment response was classified as partial response, stable disease, or progressive disease. A Cox proportional hazards model was used to correlate baseline CT features and EGFR mutations with progression-free survival (PFS) and overall survival. Results: All patients underwent TKI therapy after identifying exon mutations in the EGFR gene, comprising exon 19 deletion (19del) ( $n = 77$ ), L858R ( $n = 43$ ), and exon 18 ( $n = 10$ ). Outcomes were partial response ( $n = 103$ ), stable disease ( $n = 22$ ), and progressive disease ( $n = 5$ ). In univariate analysis, PFS was significantly longer with small lesions (hazard ratio [HR], 1.02; 95% confidence interval [CI]: 1.01, 1.03;  $P < .01$ ), nodular main lesions (HR, 0.55; 95% CI: 0.34, 0.88;  $P = .01$ ), or peripheral lesions (HR, 0.62; 95% CI: 0.42, 0.93;  $P = .02$ ). In univariate analysis, PFS was significantly longer with smaller lesions (HR, 1.02; 95% CI: 1.01, 1.03;  $P < .01$ ), nodular main lesions (HR, 0.55; 95% CI: 0.34, 0.88;  $P = .01$ ), peripheral

lesions (HR, 0.62; 95% CI: 0.42, 0.93; P = .02), 19del (HR, 0.33; 95% CI: 0.14, 0.77; P = .01), or L858R (HR, 0.39; 95% CI: 0.16, 0.97; P = .04). In multivariate analysis, PFS was significantly longer with 19del (HR, 0.30; 95% CI: 0.11, 0.84; P = .02) and shorter with scattered metastases (HR, 2.25; 95% CI: 1.44, 5.51; P < .01). Conclusion: Smaller nodular lesions, peripheral lesions, and 19del relate to longer PFS after EGFR TKI treatment. © RSNA, 2013.

[176]

**TÍTULO / TITLE:** - Association between Expression of X-linked Inhibitor of Apoptosis Protein and the Clinical Outcome in BRAFV600E Prevalent Papillary Thyroid Cancer Population.

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

**REVISTA / JOURNAL:** - Thyroid. 2013 Oct 15.

●● [Enlace al texto completo \(gratis o de pago\) 1089/thy.2012.0585](#)

**AUTORES / AUTHORS:** - Yim JH; Kim WG; Jeon M; Han JM; Kim TY; Yoon JH; Hong SJ; Song DE; Gong G; Shong Y; Kim WB

**INSTITUCIÓN / INSTITUTION:** - Asan Medical Center, University of Ulsan College of Medicine, Internal Medicine, Seoul, Korea, Republic of ; [wisdomyim@gmail.com](mailto:wisdomyim@gmail.com).

**RESUMEN / SUMMARY:** - Background: The X-linked inhibitor of apoptosis protein (XIAP) is associated with carcinogenesis, cancer progression and metastasis through inhibition of the caspase-mediated apoptotic pathway. The BRAFV600E mutation is the most common genetic alteration and an established prognostic marker in papillary thyroid cancer (PTC). The prevalence of the BRAF mutation is very high up to 80% in Korean PTC patients. In the present study, we evaluated the potential role of the XIAP expression as a novel prognostic marker to predict recurrence, in combination with the BRAFV600E mutational status. Methods: The study enrolled 164 patients with conventional PTC who underwent bilateral thyroidectomy followed by immediate I-131 ablation. The presence of the BRAFV600E mutation was evaluated by direct sequencing. The degree of XIAP protein expression was evaluated by immunohistochemical (IHC) staining using monoclonal antibody. Results: The BRAFV600E mutation was found in 123 of 164 patients (75%) with conventional PTC. XIAP expression was positive in 128 of 164 patients (75%), and positive XIAP expression was significantly associated with the presence of lateral cervical lymph node metastases ( $p=0.01$ ). XIAP expression was more frequent in BRAFV600E mutated PTCs than that in BRAF wild type PTCs ( $p=0.048$ ). The BRAFV600E mutation was significantly associated with cancer recurrence in study subjects (HR=2.98,  $p=0.039$ ). PTCs positive for the BRAFV600E mutation, but negative for XIAP expression had a significantly higher rate of recurrent PTC (HR=4.53,  $p=0.012$ ). Conclusion: The evaluation of the XIAP expression and BRAF mutational analysis was more useful for the prediction of cancer recurrence in patients with PTC than BRAF genotype alone.

[177]

**TÍTULO / TITLE:** - Ubiquitination-Deubiquitination by the TRIM27-USP7 Complex Regulates Tumor Necrosis Factor Alpha-Induced Apoptosis.

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

**REVISTA / JOURNAL:** - Mol Cell Biol. 2013 Dec;33(24):4971-84. doi: 10.1128/MCB.00465-13. Epub 2013 Oct 21.

●● Enlace al texto completo (gratis o de pago) [1128/MCB.00465-13](https://doi.org/10.1128/MCB.00465-13)

**AUTORES / AUTHORS:** - Zaman MM; Nomura T; Takagi T; Okamura T; Jin W; Shinagawa T; Tanaka Y; Ishii S

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Molecular Genetics, RIKEN Tsukuba Institute, Tsukuba, Ibaraki, Japan.

**RESUMEN / SUMMARY:** - Tumor necrosis factor alpha (TNF-alpha) plays a role in apoptosis and proliferation in multiple types of cells, and defects in TNF-alpha-induced apoptosis are associated with various autoimmune diseases. Here, we show that TRIM27, a tripartite motif (TRIM) protein containing RING finger, B-box, and coiled-coil domains, positively regulates TNF-alpha-induced apoptosis. Trim27-deficient mice are resistant to TNF-alpha-d-galactosamine-induced hepatocyte apoptosis. Trim27-deficient mouse embryonic fibroblasts (MEFs) are also resistant to TNF-alpha-cycloheximide-induced apoptosis. TRIM27 forms a complex with and ubiquitinates the ubiquitin-specific protease USP7, which deubiquitinates receptor-interacting protein 1 (RIP1), resulting in the positive regulation of TNF-alpha-induced apoptosis. Our findings indicate that the ubiquitination-deubiquitination cascade mediated by the TRIM27-USP7 complex plays an important role in TNF-alpha-induced apoptosis.

[178]

**TÍTULO / TITLE:** - MRI predictive factors for tumor response in rectal cancer following neoadjuvant chemoradiation therapy—implications for induction chemotherapy?

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

**REVISTA / JOURNAL:** - Int J Radiat Oncol Biol Phys. 2013 Nov 1;87(3):505-11. doi: 10.1016/j.ijrobp.2013.06.2052.

●● Enlace al texto completo (gratis o de pago) [1016/j.ijrobp.2013.06.2052](https://doi.org/10.1016/j.ijrobp.2013.06.2052)

**AUTORES / AUTHORS:** - Yu SK; Tait D; Chau I; Brown G

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**RESUMEN / SUMMARY:** - **PURPOSE:** Clinical and magnetic resonance imaging (MRI) characteristics at baseline and following chemoradiation therapy (CRT) most strongly associated with histopathologic response were investigated and survival outcomes evaluated in accordance with imaging and pathological response. **METHODS AND MATERIALS:** Responders were defined as mrT3c/d-4 downstaged to ypT0-2 on pathology or low at risk mrT2 downstaged to ypT1 or T0. Multivariate logistic regression of baseline and posttreatment MRI: T, N, extramural venous invasion (EMVI), circumferential resection margin, craniocaudal length <5 cm, and MRI tumor height <=5 cm were used to identify independent predictor(s) for response. An association between induction chemotherapy and EMVI status was analyzed. Survival outcomes for pathologic and MRI responders and nonresponders were analyzed. **RESULTS:** Two hundred eighty-one patients were eligible; 114 (41%) patients were pathology responders. Baseline MRI negative EMVI (odds ratio 2.94, P=.007), tumor height <=5 cm (OR 1.96, P=.02), and mrEMVI status change (positive to negative) following CRT (OR 3.09, P<.001) were the only predictors for response. There was a strong association detected between induction chemotherapy and ymrEMVI status change after CRT (OR 9.0, P<.003). ymrT0-2 gave a positive predictive value of 80%

and OR of 9.1 for ypT0-2. ymrN stage accuracy of ypN stage was 75%. Three-year disease-free survival for pathology and MRI responders were similar at 80% and 79% and significantly better than poor responders. CONCLUSIONS: Tumor height and mrEMVI status are more important than baseline size and stage of the tumor as predictors of response to CRT. Both MRI- and pathologic-defined responders have significantly improved survival. "Good response" to CRT in locally advanced rectal cancer with ypT0-2 carries significantly better 3-year overall survival and disease-free survival. Use of induction chemotherapy for improving mrEMVI status and knowledge of MRI predictive factors could be taken into account in the pursuit of individualized neoadjuvant treatments for patients with rectal cancer.

[179]

**TÍTULO / TITLE:** - RNA-seq identifies clinically relevant fusion genes in leukemia including a novel MEF2D/CSF1R fusion responsive to imatinib.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Nov 4. doi: 10.1038/leu.2013.324.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.324](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Genetics, University and Regional Laboratories, Lund University, Lund, Sweden.

[180]

**TÍTULO / TITLE:** - Hallmarks of aromatase inhibitor drug resistance revealed by epigenetic profiling in breast cancer.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Nov 15;73(22):6632-41. doi: 10.1158/0008-5472.CAN-13-0704.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-0704](#)

**AUTORES / AUTHORS:** - Jansen MP; Knijnenburg T; Reijm EA; Simon I; Kerkhoven R; Droog M; Velds A; van Laere S; Dirix L; Alexi X; Foekens JA; Wessels L; Linn SC; Berns EM; Zwart W

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Medical Oncology, Erasmus University Medical Center, Cancer Institute, Rotterdam; Departments of Molecular Carcinogenesis and Molecular Pathology, Central Genomic Facility, the Netherlands Cancer Institute; Agendia NV, Amsterdam, the Netherlands; and Translational Cancer Research Unit, Laboratory of Pathology, Antwerp University/Oncology Centre, GZA Hospitals St-Augustinus, Antwerp, Belgium.

**RESUMEN / SUMMARY:** - Aromatase inhibitors are the major first-line treatment of estrogen receptor-positive breast cancer, but resistance to treatment is common. To date, no biomarkers have been validated clinically to guide subsequent therapy in these patients. In this study, we mapped the genome-wide chromatin-binding profiles of estrogen receptor alpha (ERalpha), along with the epigenetic modifications H3K4me3 and H3K27me3, that are responsible for determining gene transcription (n = 12). Differential binding patterns of ERalpha, H3K4me3, and H3K27me3 were enriched

between patients with good or poor outcomes after aromatase inhibition. ERalpha and H3K27me3 patterns were validated in an additional independent set of breast cancer cases (n = 10). We coupled these patterns to array-based proximal gene expression and progression-free survival data derived from a further independent cohort of 72 aromatase inhibitor-treated patients. Through this approach, we determined that the ERalpha and H3K27me3 profiles predicted the treatment outcomes for first-line aromatase inhibitors. In contrast, the H3K4me3 pattern identified was not similarly informative. The classification potential of these genes was only partially preserved in a cohort of 101 patients who received first-line tamoxifen treatment, suggesting some treatment selectivity in patient classification. Cancer Res; 73(22); 6632-41. ©2013 AACR.

[181]

**TÍTULO / TITLE:** - Successful treatment with a combination of electrocautery using wire snares and gefitinib in patients with EGFR-mutant lung cancer and central airway obstruction.

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

**REVISTA / JOURNAL:** - Intern Med. 2013;52(20):2331-5.

**AUTORES / AUTHORS:** - Araya T; Demura Y; Kasahara K; Matsuoka H; Nishitsuji M; Nishi K

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Ishikawa Prefectural Central Hospital, Japan.

**RESUMEN / SUMMARY:** - One-third of lung cancer patients present with life-threatening central airway obstruction (CAO). Two elderly patients were referred to our institution with symptoms caused by CAO. In each case, thoracic computed tomography and a bronchoscopic examination revealed a tumor obstructing the central airway. The tumors were resected endoscopically, and the patients' respiratory and performance status remarkably improved. Both patients were diagnosed with an advanced stage of lung adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutations. They received gefitinib monotherapy, with partial responses sustained for more than 12 months. Combination therapy with endoscopic tumor resection and gefitinib is beneficial in patients with EGFR-mutant lung cancer and CAO.

[182]

**TÍTULO / TITLE:** - Safety and tolerability of intrathecal liposomal cytarabine as central nervous system prophylaxis in patients with acute lymphoblastic leukemia.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Nov 25.

●● [Enlace al texto completo \(gratis o de pago\) 3109/10428194.2013.853765](#)

**AUTORES / AUTHORS:** - Valentin A; Troppan K; Pfeilstocker M; Nosslinger T; Linkesch W; Neumeister P

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology, Medical University Graz , Austria.

**RESUMEN / SUMMARY:** - Central nervous system recurrence in acute lymphoblastic leukemia (ALL) occurs in up to 15% of patients and is frequently associated with poor outcome. The purpose of our study was to evaluate the efficacy and safety of a slow-

release liposomal formulation of cytarabine for intrathecal (IT) meningeal prophylaxis in patients suffering from ALL. Forty patients aged 20-77 years (median 36) were preventively treated with a total of 96 (range 1-6) single doses containing 50 mg of liposomal cytarabine on a compassionate use basis. After a median observation period of 23 months (range 2-118) only two patients experienced a combined medullary-leptomeningeal disease recurrence after primary diagnosis. Except for headache grade 2 in two patients, no specific toxicity attributable to IT liposomal cytarabine application was noted. Long-term neurological side effects were not observed. IT liposomal cytarabine therapy with concomitant dexamethasone appears to be feasible and well tolerated.

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[183]

**TÍTULO / TITLE:** - CYP3A5\*3 and bilirubin predict midazolam population pharmacokinetics in Asian cancer patients.

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

**REVISTA / JOURNAL:** - J Clin Pharmacol. 2013 Nov 11. doi: 10.1002/jcph.230.

●● [Enlace al texto completo \(gratis o de pago\) 1002/jcph.230](#)

**AUTORES / AUTHORS:** - Seng KY; Hee KH; Soon GH; Sapari NS; Soong R; Goh BC; Lee LS

**INSTITUCIÓN / INSTITUTION:** - Yong Loo Lin School of Medicine, National University of Singapore, Singapore; Defence Medical & Environmental Research Institute, DSO National Laboratories, Singapore.

**RESUMEN / SUMMARY:** - We aim to evaluate the influence of covariates, including cytochrome P450 3A (CYP3A) genetic polymorphisms, on the pharmacokinetics of midazolam (MDZ) in Asian cancer patients, using a population pharmacokinetic approach. Pharmacokinetic data were obtained from twenty-four adult cancer patients who received an intravenous bolus dose of 1mg MDZ as a CYP3A phenotyping probe, one day before starting FOLFIRI chemotherapy. Concentrations of MDZ and its major metabolites, 1'-hydroxymidazolam (1OHM) and 1'-hydroxymidazolam glucuronide (HMG) were measured using liquid chromatography/mass spectrometry. The population pharmacokinetic study was conducted using NONMEM. Demographics, clinical characteristics and genetic polymorphisms were screened as covariates. A two-compartment model for MDZ and two sequential compartments representing 1OHM and HMG best described the data. The CYP3A5\*3 and total bilirubin level significantly influenced MDZ clearance. The population typical MDZ clearance for CYP3A5\*3 expressers was 22% lower than non-expressers. Baseline bodyweight was a statistically significant covariate for clearance and distribution volume of 1OHM. Creatinine clearance was positively correlated with HMG clearance. Our data indicate that CYP3A5\*3, total bilirubin, bodyweight and creatinine clearance are important predictors of MDZ and metabolite pharmacokinetics. Further studies in more patients are needed to explore the links between the identified covariates and the disposition of MDZ and its metabolites.

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[184]

**TÍTULO / TITLE:** - Overexpression of pituitary tumor transforming gene (PTTG) is associated with tumor progression and poor prognosis in patients with esophageal squamous cell carcinoma.

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

**REVISTA / JOURNAL:** - Acta Histochem. 2013 Oct 28. pii: S0065-1281(13)00191-8. doi: 10.1016/j.acthis.2013.09.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.acthis.2013.09.011](#)

**AUTORES / AUTHORS:** - Zhang J; Yang Y; Chen L; Zheng D; Ma J

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, The Third Affiliated Hospital of Harbin Medical University, Harbin 150081, People's Republic of China.

**RESUMEN / SUMMARY:** - Pituitary tumor transforming gene (PTTG) is a newly identified proto-oncogene that has been shown to be aberrantly overexpressed in a subset of human cancers. The aim of the present study was to examine PTTG expression in patients with esophageal squamous cell cancer (ESCC) and explore its clinical significance. PTTG protein expression was analyzed in 108 archived, paraffin-embedded primary ESCC specimens by immunohistochemistry and correlated with clinicopathological parameters and patients' outcome. Overexpression of PTTG was observed in 38.0% (41/108) of primary ESCC tissues and significantly correlated with differentiation, TNM stage, lymph node metastasis, and depth of invasion ( $P < 0.05$ ). Kaplan-Meier curves showed that ESCC patients with tumors expressing high levels of PTTG had substantially shorter overall survival compared with patients expressing low levels of PTTG ( $P = 0.022$ , log-rank test). Cox multivariate regression analysis revealed that overexpression of PTTG was an independent prognostic factor in overall survival for ESCC patients (hazard ratio was 2.35,  $P = 0.009$ ). Overall, our data suggest that overexpression of PTTG may contribute to the malignant progression of ESCC and serve as a novel prognostic indicator for patients with ESCC.

[185]

**TÍTULO / TITLE:** - C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):5065-74.

**AUTORES / AUTHORS:** - Toiyama Y; Inoue Y; Saigusa S; Kawamura M; Kawamoto A; Okugawa Y; Hiro J; Tanaka K; Mohri Y; Kusunoki M

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Graduate School of Medicine, Mie University, Mie 514-8507, Japan. [ytoi0725@clin.medic.mie-u.ac.jp](mailto:ytoi0725@clin.medic.mie-u.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The clinical significance of the systemic inflammatory response (SIR) in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy (CRT), to the best of our knowledge, has not been thus far investigated. PATIENTS AND METHODS: The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and C-Reactive protein (CRP) levels for 84 patients with rectal cancer undergoing CRT were available as indicators of SIR status. The impact of SIR status on the prognosis of these patients was assessed. RESULTS: Elevated NLR, CRP, carcinoembryonic antigen (CEA) and pathological TNM stage III [ypN(+)] were identified as significant prognostic factors for poor overall survival (OS), with CRP and ypN(+) being validated as independent predictors of OS. Elevated CRP

and CEA levels were significant predictive factors for poor disease-free survival (DFS), and an elevated CRP level was identified as the only independent predictive factor for DFS. In addition, an elevated CRP level predicted for poorer OS and DFS in patients with pathological TNM stage I-II [ypN(-)]. CONCLUSION: CRP is a promising predictor of recurrence and prognosis in patients with rectal cancer treated by CRT.

[186]

**TÍTULO / TITLE:** - The enhanced apoptosis and antiproliferative response to combined treatment with valproate and nicotinamide in MCF-7 breast cancer cells.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 10.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1356-0](#)

**AUTORES / AUTHORS:** - Jafary H; Ahmadian S; Soleimani M

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Institute of Biochemistry and Biophysics, University of Tehran, P.O. Box 13145-1384, Tehran, Iran.

**RESUMEN / SUMMARY:** - Acetylation of histone is a major player in epigenetic modifications, resulting in open chromatin structures and, hence, permissive conditions for transcription-factor recruitment to the promoters, followed by initiation of transcription. Histone deacetylase inhibitors arrest cancer cell growth and cause apoptosis with low toxicity thereby constituting a promising treatment for cancer. In this study, we examined the antiproliferative effects of valproate with a combination of nicotinamide in the MCF-7 cell line. MCF-7 was treated with various concentrations of valproate. The MTT assay showed that the viability of MCF-7 cells was inhibited and the cell activity was decreased. Viability percent of valproate and nicotinamide combined treatment cells (28 +/- 2) was 1.78 times increased compared with the valproate-alone (0.5 mM) treated cells (50 +/- 2). Colony formation in soft agar indicated that valproate at 0.3 mM, when used alone, weakly suppressed proliferation of cells (82 +/- 3) and the combination treatment of valproate + nicotinamide strongly suppressed cell proliferation (51 +/- 3). The flow cytometric and microscopic analyses of HDAC1 combined with treated cells indicated strong apoptosis induction and nuclear morphological alterations greater than those of valproate alone. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis confirmed the efficiency of the HDAC inhibitor combination, revealing the effectively upregulated p16 and p21. Furthermore, to investigate the role of acetyl-histone H3 levels, western blot analyses have been performed and high levels of acetylated histone H3 were detected in valproate- and nicotinamide-treated cells. These results suggest that the combination treatment of valproate with nicotinamide exerts significant antitumor activity and could be a promising therapeutic candidate to treat human breast cancer.

[187]

**TÍTULO / TITLE:** - Role of the EphB2 receptor in autophagy, apoptosis and invasion in human breast cancer cells.

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

**REVISTA / JOURNAL:** - Exp Cell Res. 2013 Nov 6. pii: S0014-4827(13)00472-2. doi: 10.1016/j.yexcr.2013.10.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.yexcr.2013.10.022](#)

**AUTORES / AUTHORS:** - Chukkapalli S; Amessou M; Dilly AK; Dekhil H; Zhao J; Liu Q; Bejna A; Thomas RD; Bandyopadhyay S; Bismar TA; Neill D; Azoulay L; Batist G; Kandouz M

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Wayne State University School of Medicine, Detroit, MI, USA.

**RESUMEN / SUMMARY:** - The Eph and Ephrin proteins, which constitute the largest family of receptor tyrosine kinases, are involved in normal tissue development and cancer progression. Here, we examined the expression and role of the B-type Eph receptor EphB2 in breast cancers. By immunohistochemistry using a progression tissue microarray of human clinical samples, we found EphB2 to be expressed in benign tissues, but strongly increased in cancers particularly in invasive and metastatic carcinomas. Subsequently, we found evidence that EphB2, whose expression varies in established cell breast lines, possesses multiple functions. First, the use of a DOX-inducible system to restore EphB2 function to low expressers resulted in decreased tumor growth in vitro and in vivo, while its siRNA-mediated silencing in high expressers increased growth. This function involves the onset of apoptotic death paralleled by caspases 3 and 9 activation. Second, EphB2 was also found to induce autophagy, as assessed by immunofluorescence and/or immunoblotting examination of the LC3, ATG5 and ATG12 markers. Third, EphB2 also has a pro-invasive function in breast cancer cells that involves the regulation of MMP2 and MMP9 metalloproteases and can be blocked by treatment with respective neutralizing antibodies. Furthermore, EphB2-induced invasion is kinase-dependent and is impeded in cells expressing a kinase-dead mutant EphB2. In summary, we identified a mechanism involving a triple role for EphB2 in breast cancer progression, whereby it regulates apoptosis, autophagy, and invasion.

[188]

**TÍTULO / TITLE:** - Pharmacogenetic effects of regulatory nuclear receptors (PXR, CAR, RXRalpha and HNF4alpha) on docetaxel disposition in Chinese nasopharyngeal cancer patients.

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

**REVISTA / JOURNAL:** - Eur J Clin Pharmacol. 2013 Nov 6.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00228-013-1596-3](#)

**AUTORES / AUTHORS:** - Chew SC; Lim J; Singh O; Chen X; Tan EH; Lee EJ; Chowbay B

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Drive, Singapore, Singapore, 117597.

**RESUMEN / SUMMARY:** - PURPOSE: This exploratory study was aimed at elucidating the pharmacogenetics of regulatory nuclear receptors (PXR, CAR, RXRalpha and HNF4alpha) and their implications on docetaxel pharmacokinetics and pharmacodynamics in local Chinese nasopharyngeal cancer patients. METHODS: A total of 59 single nucleotide polymorphisms (SNPs), including tag-SNPs and functionally relevant SNPs of the genes encoding these regulatory nuclear receptors (PXR/NR112, CAR/NR113, RXRalpha/NR2B1 and HNF4alpha/NR2A1), were profiled in the patients enrolled in our study by direct sequencing (N = 50). The generalized linear model was employed to estimate the haplotypic effects on the pharmacokinetics and

pharmacodynamics of the patients. RESULTS: The pharmacokinetic profiles of docetaxel in these patients were characterized by marked interindividual variability, with approximately four- to sixfold variations observed in Cmax, AUC0-infinity and CL. Individual SNP association tests revealed that polymorphisms in NR2B1 and NR2A1 were significantly correlated with altered docetaxel pharmacokinetics. Subsequent haplotype association analysis identified the NR2B1 LD block 2 AG haplotype [\*+4458G>A(rs3132291) and \*+4988A>G(rs4842198)] to be significantly associated with altered pharmacokinetics, in which patients carrying two copies of the AG haplotype had approximately a 20 % decreased Cmax and AUC0-infinity and a 21 % increased CL compared to those who carried only one copy or no copies of the haplotype. A number of SNPs in NR112, NR113, NR2B1 and NR2A1 were also associated with a significant decrease in blood counts from baseline. No haplotype was found to exert any effects on the pharmacodynamics parameters. CONCLUSIONS: The present exploratory study identified several SNPs in the genes encoding regulatory nuclear receptors which may account for the interpatient variability in docetaxel pharmacokinetics and pharmacodynamics. These findings highlight the important role of regulatory nuclear receptors on the disposition of docetaxel.

[189]

**TÍTULO / TITLE:** - MYB down-regulation enhances sensitivity of U937 myeloid leukemia cells to the histone deacetylase inhibitor LBH589 in vitro and in vivo.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Sep 26. pii: S0304-3835(13)00691-5. doi: 10.1016/j.canlet.2013.09.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.09.022](#)

**AUTORES / AUTHORS:** - Ye P; Zhao L; McGirr C; Gonda TJ

**INSTITUCIÓN / INSTITUTION:** - School of Pharmacy, The University of Queensland, Brisbane, Queensland 4102, Australia; The University of Queensland Diamantina Institute, Brisbane, Queensland 4102, Australia.

**RESUMEN / SUMMARY:** - The effect of combining MYB suppression with the histone deacetylase inhibitor LBH589 was studied in human myeloid leukemia cell lines. MYB knockdown inhibited proliferation and induced apoptosis in U937 and K562 cells in vitro, and also sensitized both to the pro-apoptotic effect of LBH589. This was accompanied by enhanced expression of the pro-apoptotic BCL2 family members BOK and BIM. U937 cells carrying inducible MYB shRNA were also transplanted into NOD/SCID mice. The combination of MYB knockdown and LBH589 prolonged survival compared to either treatment alone, suggesting that further development of such combinations might lead to effective and safe leukemia therapies.

[190]

**TÍTULO / TITLE:** - High expressions of galectin-1 and VEGF are associated with poor prognosis in gastric cancer patients.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 16.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1332-8](#)

**AUTORES / AUTHORS:** - Chen J; Tang D; Wang S; Li QG; Zhang JR; Li P; Lu Q; Niu G; Gao J; Ye NY; Wang DR

**INSTITUCIÓN / INSTITUTION:** - Department of Gastric Cancer and Soft Tissue Sarcomas, Fudan University Shanghai Cancer Center, Shanghai, 200032, China.

**RESUMEN / SUMMARY:** - High expressions of galectin-1 and vascular endothelial growth factor (VEGF) are correlated with biological behavior in some cancers. The aim of this study is to evaluate the expressions of galectin-1 and VEGF in gastric cancer and investigate their relationships with clinicopathological factors and prognostic significance. Immunohistochemical analyses for galectin-1 and VEGF expression were performed on 108 cases of gastric cancer. The relationship between the expression and staining intensity of galectin-1 and VEGF, clinicopathological variables, and survival rates was analyzed. Immunohistochemical staining demonstrated that 68 of 108 gastric cancer samples (63.0 %) were positive for galectin-1 and 62 out of 108 gastric cancer samples (57.4 %) were positive for VEGF. Galectin-1 expression was associated with tumor size, differentiation grade, TNM stage, lymph node metastases, and VEGF expression. VEGF expression was related to tumor size, TNM stage, and lymph node metastases. Kaplan-Meier survival analysis showed that high galectin-1 and VEGF expressions exhibited significant correlations with poor prognosis for gastric cancer patients. Multivariate analysis revealed that galectin-1 and VEGF expressions were independent prognostic parameters for the overall survival rate of gastric cancer patients. The results of the present study suggest that galectin-1 expression is positively associated with VEGF expression. Both galectin-1 and VEGF can serve as independent prognostic indicators of poor survival for gastric cancer.

[191]

**TÍTULO / TITLE:** - Heme oxygenase-1 expression in human gliomas and its correlation with poor prognosis in patients with astrocytoma.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 15.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1373-z](#)

**AUTORES / AUTHORS:** - Gandini NA; Fermento ME; Salomon DG; Obiol DJ; Andres NC; Zenklusen JC; Arevalo J; Blasco J; Lopez Romero A; Facchinetti MM; Curino AC

**INSTITUCIÓN / INSTITUTION:** - Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas Bahía Blanca (INIBIBB-CONICET), Camino La Carrindanga Km 7, 8000, Bahía Blanca, Argentina.

**RESUMEN / SUMMARY:** - In human glioma tumors, heme oxygenase-1 (HO-1) has been shown to be upregulated both when compared with normal brain tissues and also during oligodendroglioma progression. The cell types that express HO-1 have been shown to be mainly macrophages/microglia and T cells. However, many other reports also demonstrated that cell lines derived from glioma tumors and astrocytes express HO-1 after the occurrence of a wide variety of cell injuries and stressors. In addition, the significance of HO-1 upregulation in glioma had not, so far, been addressed. We therefore aimed at investigating the expression and significance of HO-1 in human glial tumors. For this purpose, we performed a wide screening of HO-1 expression in gliomas by using tissue microarrays containing astrocytomas, oligodendrogliomas, mixed tumors, and normal brain tissues. We subsequently correlated protein expression with patient clinicopathological data. We found

differences in HO-1 positivity rates between non-malignant brain (22 %) and gliomas (54 %,  $p = 0.01$ ). HO-1 was expressed by tumor cells and showed cytoplasmic localization, although 19 % of tumor samples also depicted nuclear staining. Importantly, a significant decrease in the overall survival time of grade II and III astrocytoma patients with HO-1 expression was observed. This result was validated at the mRNA level in a cohort of 105 samples. However, no association of HO-1 nuclear localization with patient survival was detected. In vitro experiments aimed at investigating the role of HO-1 in glioma progression showed that HO-1 modulates glioma cell proliferation, but has no effects on cellular migration. In conclusion, our results corroborate the higher frequency of HO-1 protein expression in gliomas than in normal brain, demonstrate that HO-1 is expressed by glial malignant cells, and show an association of HO-1 expression with patients' shorter survival time.

[192]

**TÍTULO / TITLE:** - Gene Expression Profiling to Predict Viridans Group Streptococcal and Invasive Fungal Infection in Pediatric Acute Myeloid Leukemia: A Brief Report from the Children's Oncology Group.

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

**REVISTA / JOURNAL:** - Acta Haematol. 2013 Nov 6;131(3):167-169.

●● [Enlace al texto completo \(gratis o de pago\) 1159/000353758](#)

**AUTORES / AUTHORS:** - Lee GE; Sung L; Fisher BT; Sullivan KE; McWilliams T; Tobias JW; Meshinchi S; Alonzo TA; Gamis A; Aplenc R

**INSTITUCIÓN / INSTITUTION:** - Division of Infectious Diseases, The Children's Hospital of Philadelphia, Philadelphia, Pa., USA.

[193]

**TÍTULO / TITLE:** - AXL is a key regulator of inherent and chemotherapy-induced invasion and predicts a poor clinical outcome in early stage colon cancer.

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

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

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-1354](#)

**AUTORES / AUTHORS:** - Dunne P; McArt DG; Blayney JK; Kalimutho M; Greer S; Wang T; Srivastava S; Ong CW; Arthur KJ; Loughrey M; Redmond K; Longley DB; Salto-Tellez M; Johnston PG; Van Schaeybroeck S

**INSTITUCIÓN / INSTITUTION:** - Oncology, Queen's University Belfast.

**RESUMEN / SUMMARY:** - PURPOSE: Despite the use of 5-FU-based adjuvant treatments, a large proportion of high risk stage II/III colorectal cancer (CRC) patients will relapse. Thus, novel therapeutic strategies are needed for early stage CRC. Residual micrometastatic disease from the primary tumour is a major cause of patient relapse. EXPERIMENTAL DESIGN: In order to model CRC tumour cell invasion/metastasis, we have generated invasive (KRASMT/KRASWT/+chr3/p53-null) CRC cell subpopulations. Receptor tyrosine kinase (RTK) screens were used to identify novel proteins which underpin the migratory/invasive phenotype. Migration/invasion was assessed using the XCELLigence system. Tumours from patients with early stage CRC (N=336) were examined for AXL expression. RESULTS:

Invasive CRC cell subpopulations showed a transition from an epithelial-to-mesenchymal like phenotype with significant increases in migration, invasion, colony-forming ability and an attenuation of EGFR/HER2 autocrine signalling. Receptor tyrosine kinase arrays showed significant increases in AXL levels in all invasive sub-lines. Importantly, 5-FU treatment resulted in significantly increased migration and invasion and targeting AXL using pharmacologic inhibition or RNAi approaches, suppressed basal and 5-FU-induced migration and invasion. Significantly, high AXL mRNA and protein expression were found to be associated with poor overall survival in early stage CRC tissues. CONCLUSIONS: We have identified AXL as poor prognostic marker and important mediator of cell migration/invasiveness in CRC. These findings provide support for the further investigation of AXL as a novel prognostic biomarker and therapeutic target in CRC, in particular in the adjuvant disease where EGFR/VEGF-targeted therapies have failed.

[194]

**TÍTULO / TITLE:** - The induction of heme oxygenase-1 suppresses heat shock protein 90 and the proliferation of human breast cancer cells through its byproduct carbon monoxide.

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

**REVISTA / JOURNAL:** - Toxicol Appl Pharmacol. 2013 Nov 6. pii: S0041-008X(13)00475-4. doi: 10.1016/j.taap.2013.10.027.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.taap.2013.10.027](#)

**AUTORES / AUTHORS:** - Lee WY; Chen YC; Shih CM; Lin CM; Cheng CH; Chen KC; Lin CW

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Chi-Mei Hospital, Tainan, Taiwan; Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - Heme oxygenase (HO)-1 is an oxidative stress-response enzyme which catalyzes the degradation of heme into bilirubin, ferric ion, and carbon monoxide (CO). Induction of HO-1 was reported to have antitumor activity; the inhibitory mechanism, however, is still unclear. In the present study, we found that treatment with [Ru(CO)<sub>3</sub>Cl<sub>2</sub>]<sub>2</sub> (RuCO), a CO-releasing compound, reduced the growth of human MCF7 and MDA-MB-231 breast cancer cells. Analysis of growth-related proteins showed that treatment with RuCO down-regulated cyclinD1, CDK4, and hTERT protein expressions. Interestingly, RuCO treatment resulted in opposite effects on wild-type and mutant p53 proteins. These results were similar to those of cells treated with geldanamycin (a heat shock protein (HSP)90 inhibitor), suggesting that RuCO might affect HSP90 activity. Moreover, RuCO induced mutant p53 protein destabilization accompanied by promotion of ubiquitination and proteasome degradation. The induction of HO-1 by cobalt protoporphyrin IX (CoPP) showed consistent results, while the addition of tin protoporphyrin IX (SnPP), an HO-1 enzymatic inhibitor, diminished the RuCO-mediated effect. RuCO induction of HO-1 expression was reduced by a p38 mitogen-activated protein kinase inhibitor (SB203580). Additionally, treatment with a chemopreventive compound, curcumin, induced HO-1 expression accompanied with reduction of HSP90 client protein expression. The induction of HO-1 by curcumin inhibited 12-O-tetradecanoyl-13-acetate (TPA)-elicited matrix metalloproteinase-9 expression and tumor invasion. In

conclusion, we provide novel evidence underlying HO-1's antitumor mechanism. CO, a byproduct of HO-1, suppresses HSP90 protein activity, and the induction of HO-1 may possess potential as a cancer therapeutic.

[195]

**TÍTULO / TITLE:** - Emetine enhances the tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis of pancreatic cancer cells by downregulation of myeloid cell leukemia sequence-1 protein.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):456-62. doi: 10.3892/or.2013.2838. Epub 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2838](#)

**AUTORES / AUTHORS:** - Han Y; Park S; Kinyua AW; Andera L; Kim KW; Kim I

**INSTITUCIÓN / INSTITUTION:** - Asan Institute for Life Sciences, Asan Medical Center, Seoul 138-736, Republic of Korea.

**RESUMEN / SUMMARY:** - Although the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising cancer therapeutic agent, it shows limited efficacy in human pancreatic cancer cells. Protein synthesis inhibition has been reported to sensitize cancer cells to apoptosis-inducing agents, but the detailed mechanism by which protein synthesis inhibition sensitizes cells to TRAIL has not been determined. To investigate the mechanism underlying pancreatic cancer cell resistance to TRAIL, we performed a small scale high-throughput compound screening in AsPC-1 pancreatic cancer cells using a bioactive small molecule library. We identified 8 compounds that reproducibly sensitize AsPC-1 cells to TRAIL-induced apoptosis. One of these compounds, emetine hydrochloride, when combined with subtoxic concentrations of TRAIL, induced massive apoptosis in AsPC-1 and BxPC-3 pancreatic cancer cells. Cell death analysis revealed that the sensitizing effects of emetine were specific to TRAIL. Emetine downregulated the expression of the TRAIL-related anti-apoptotic protein Mcl-1 in a dose- and time-dependent manner. Furthermore, specific knockdown of Mcl-1 using small interfering RNA without emetine treatment sensitized pancreatic cancer cells to TRAIL. Emetine sensitization of pancreatic cancer cells to TRAIL via Mcl-1 was confirmed under hypoxic conditions. Taken together, these findings strongly suggest that Mcl-1 is involved in pancreatic cancer cell resistance to TRAIL, and emetine facilitates the apoptosis of TRAIL-tolerant pancreatic cancer cells by specifically inhibiting Mcl-1 function.

[196]

**TÍTULO / TITLE:** - Hepatitis B Virus Inhibits Apoptosis of Hepatoma Cells by Sponging the MicroRNA 15a/16 Cluster.

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

**REVISTA / JOURNAL:** - J Virol. 2013 Dec;87(24):13370-8. doi: 10.1128/JVI.02130-13. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1128/JVI.02130-13](#)

**AUTORES / AUTHORS:** - Liu N; Zhang J; Jiao T; Li Z; Peng J; Cui Z; Ye X

**INSTITUCIÓN / INSTITUTION:** - Center for Molecular Immunology, CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences (CAS), Beijing, China.

**RESUMEN / SUMMARY:** - Hepatitis B virus (HBV) causes chronic hepatitis in hundreds of millions of people worldwide, which can eventually lead to hepatocellular carcinoma (HCC). The molecular mechanisms underlying HBV persistence are not well understood. In this study, we found that HBV inhibited the chemotherapy drug etoposide-induced apoptosis of hepatoma cells. Further analysis revealed that HBV mRNAs possess a microRNA 15a/16 (miR-15a/16)-complementary site (HBV nucleotides [nt] 1362 to 1383) that acts as a sponge to bind and sequester endogenous miR-15a/16. Consequently, Bcl-2, known as the target of miR-15a/16, was upregulated in HBV-infected cells. The data from HBV-transgenic mice further confirmed that HBV transcripts cause the reduction of miR-15a/16 and increase of Bcl-2. More importantly, we examined the levels of HBV transcripts and miR-15a/16 in HBV-infected HCC from patients and found that the amount of HBV mRNA and the level of miR-15a/16 were negatively correlated. Consistently, the level of Bcl-2 mRNA was upregulated in HBV-infected patients. In conclusion, we identified a novel HBV mRNA-miR-15a/16-Bcl-2 regulatory pathway that is involved in inhibiting etoposide-induced apoptosis of hepatoma cells, which may contribute to facilitating chronic HBV infection and hepatoma development.

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[197]

**TÍTULO / TITLE:** - Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer.

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

**REVISTA / JOURNAL:** - J Clin Oncol. 2013 Nov 1;31(31):3987-96. doi: 10.1200/JCO.2012.45.2029. Epub 2013 Oct 7.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2012.45.2029](#)

**AUTORES / AUTHORS:** - Gainor JF; Shaw AT

**INSTITUCIÓN / INSTITUTION:** - From the Massachusetts General Hospital Cancer Center, Boston, MA.

**RESUMEN / SUMMARY:** - The success of tyrosine kinase inhibitors (TKIs) in select patients with non-small-cell lung cancer (NSCLC) has transformed management of the disease, placing new emphasis on understanding the molecular characteristics of tumor specimens. It is now recognized that genetic alterations in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) define two unique subtypes of NSCLC that are highly responsive to genotype-directed TKIs. Despite this initial sensitivity, however, the long-term effectiveness of such therapies is universally limited by the development of resistance. Identifying the mechanisms underlying this resistance is an area of intense, ongoing investigation. In this review, we provide an overview of recent experience in the field, focusing on results from preclinical resistance models and studies of patient-derived, TKI-resistant tumor specimens. Although diverse TKI resistance mechanisms have been identified within EGFR-mutant and ALK-positive patients, we highlight common principles of resistance shared between these groups. These include the development of secondary mutations in the kinase target, gene amplification of the primary oncogene, and upregulation of bypass signaling tracts. In EGFR-mutant and ALK-positive patients alike, acquired resistance

may also be a dynamic and multifactorial process that may necessitate the use of treatment combinations. We believe that insights into the mechanisms of TKI resistance in patients with EGFR mutations or ALK rearrangements may inform the development of novel treatment strategies in NSCLC, which may also be generalizable to other kinase-driven malignancies.

[198]

**TÍTULO / TITLE:** - MEN1 Gene Mutation and Reduced Expression Are Associated with Poor Prognosis in Pulmonary Carcinoids.

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

**REVISTA / JOURNAL:** - J Clin Endocrinol Metab. 2013 Nov 25.

●● Enlace al texto completo (gratis o de pago) [1210/jc.2013-2782](#)

**AUTORES / AUTHORS:** - Swarts DR; Scarpa A; Corbo V; Van Criekinge W; van Engeland M; Gatti G; Henfling ME; Papotti M; Perren A; Ramaekers FC; Speel EJ; Volante M

**INSTITUCIÓN / INSTITUTION:** - 1Departments of Molecular Cell Biology and.

**RESUMEN / SUMMARY:** - Context: MEN1 gene alterations have been implicated in lung carcinoids, but their effect on gene expression and disease outcome are unknown. Objective: To analyse MEN1 gene and expression anomalies in lung neuroendocrine neoplasms (NENs) and their correlations with clinicopathologic data and disease outcome. Design: We examined 74 lung NENs including 58 carcinoids and 16 high-grade neuroendocrine carcinomas (HGNECs) for MEN1 mutations (n=70) and allelic losses (n=69), promoter hypermethylation (n=65), and mRNA (n=74) expression. Results were correlated with disease outcome. Results: MEN1 mutations were found in 7/55 (13%) carcinoids and in 1 HGNEC, mostly associated with loss of the second allele. MEN1 decreased expression levels correlated with the presence of mutations (P=0.0060) and was also lower in HGNECs than carcinoids (P=0.0024). MEN1 methylation was not associated with mRNA expression levels. Patients with carcinoids harbouring MEN1 mutation and loss had shorter overall survival (P=0.039 and P=0.035, respectively), and low MEN1 mRNA levels correlated with distant metastasis (P=0.00010) and shorter survival (P=0.0071). In multivariate analysis, stage and MEN1 allelic loss were independent predictors of prognosis. Conclusion: Thirteen percent of pulmonary carcinoids harbour MEN1 mutation, associated with reduced mRNA expression and poor prognosis. Also in mutation-negative tumours, low MEN1 gene expression correlates with an adverse disease outcome. Hypermethylation was excluded as the underlying mechanism.

[199]

**TÍTULO / TITLE:** - Thymoquinone regulates gene expression levels in the estrogen metabolic and interferon pathways in MCF7 breast cancer cells.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2014 Jan;33(1):8-16. doi: 10.3892/ijmm.2013.1563. Epub 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1563](#)

**AUTORES / AUTHORS:** - Motaghd M; Al-Hassan FM; Hamid SS

**INSTITUCIÓN / INSTITUTION:** - Oncology and Radiological Science Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Penang 13200, Malaysia.

**RESUMEN / SUMMARY:** - New drugs are continuously being developed for the treatment of patients with estrogen receptor-positive breast cancer. Thymoquinone is one of the drugs that exhibits anticancer characteristics based on in vivo and in vitro models. This study further investigates the effects of thymoquinone on human gene expression using cDNA microarray technology. The quantification of RNA samples was carried out using an Agilent 2100 Bioanalyser to determine the RNA integrity number (RIN). The Agilent Low Input Quick Amplification Labelling kit was used to generate cRNA in two-color microarray analysis. Samples with RIN >9.0 were used in this study. The universal human reference RNA was used as the common reference. The samples were labelled with cyanine-3 (cye-3) CTP dye and the universal human reference was labelled with cyanine-5 (cye-5) CTP dye. cRNA was purified with the RNeasy Plus Mini kit and quantified using a NanoDrop 2000c spectrophotometer. The arrays were scanned data analysed using Feature Extraction and GeneSpring software. Two-step qRT-PCR was selected to determine the relative gene expression using the High Capacity RNA-to-cDNA kit. The results from Gene Ontology (GO) analysis, indicated that 8 GO terms were related to biological processes (84%) and molecular functions (16%). A total of 577 entities showed >2-fold change in expression. Of these entities, 45.2% showed an upregulation and 54.7% showed a downregulation in expression. The interpretation of single experiment analysis (SEA) revealed that the cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) and UDP glucuronosyltransferase 1 family, polypeptide A8 (UGT1A8) genes in the estrogen metabolic pathway were downregulated significantly by 43- and 11fold, respectively. The solute carrier family 7 (anionic amino acid transporter light chain, xc-system), member 11 (SLC7A11) gene in the interferon pathway, reported to be involved in the development of chemoresistance, was downregulated by 15fold. The interferon-induced protein with tetratricopeptide repeats (IFIT)1, IFIT2, IFIT3, interferon, alpha-inducible protein (IFI)6 (also known as G1P3), interferon regulatory factor 9 (IRF9, ISGF3), 2'-5'-oligoadenylate synthetase 1, 40/46 kDa (OAS1) and signal transducer and activator of transcription 1 (STAT1) genes all showed changes in expression following treatment with thymoquinone. The caspase 10, apoptosis-related cysteine peptidase (CASP10) gene was activated and the protein tyrosine phosphatase, receptor type, R (PTPRR) and myocyte enhancer factor 2C (MEF2C) genes were upregulated in the classical MAPK and p38 MAPK pathways. These findings indicate that thymoquinone targets specific genes in the estrogen metabolic and interferon pathways.

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[200]

**TÍTULO / TITLE:** - Chemotherapy-related toxicity in patients with non-metastatic Ewing sarcoma: influence of sex and age.

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

**REVISTA / JOURNAL:** - J Chemother. 2013 Jun 19.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1179/1973947813Y.000000103](#)

**AUTORES / AUTHORS:** - Paioli A; Luksch R; Fagioli F; Tamburini A; Cesari M; Palmerini E; Abate ME; Marchesi E; Balladelli A; Pratelli L; Ferrari S

**RESUMEN / SUMMARY:** - Influence of age and sex on chemotherapy-related toxicity was evaluated in children (3-9 years), adolescents (10-17 years), and adults (up to 40 years) with localized Ewing sarcoma (ES) enrolled in the ISG/SSG III protocol. Treatment was based on vincristine, doxorubicin, cyclophosphamide, ifosfamide, dactinomycin, and etoposide. High-dose chemotherapy with busulfan and melphalan was given in poor responder patients. The analysis was based on 2191 courses of standard chemotherapy and 230 patients. A lower risk of G4 leukopenia and thrombocytopenia, hospitalization, febrile neutropenia, and red blood cell (RBC) transfusions was observed in males. Use of granulocyte colony-stimulating factor (G-CSF) was more frequent in adults, while children more often received RBC transfusions. A significant correlation between sex and chemotherapy-related toxicity was observed in the study, whereas no significant differences in terms of bone marrow toxicity can be expected according to patient age. Further studies should analyse the role of pharmacokinetics, pharmacogenomics, and clinical characteristics.

[201]

**TÍTULO / TITLE:** - REST mediates androgen receptor actions on gene repression and predicts early recurrence of prostate cancer.

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

**REVISTA / JOURNAL:** - Nucleic Acids Res. 2013 Oct 24.

●● [Enlace al texto completo \(gratis o de pago\) 1093/nar/gkt921](#)

**AUTORES / AUTHORS:** - Svensson C; Ceder J; Iglesias-Gato D; Chuan YC; Pang ST; Bjartell A; Martinez RM; Bott L; Helczynski L; Ulmert D; Wang Y; Niu Y; Collins C; Flores-Morales A

**INSTITUCIÓN / INSTITUTION:** - Novo Nordisk Foundation Center for Protein Research, Faculty of Health Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark, Division of Urological Cancers, Department of Clinical Sciences, Skane University Hospital, Lund University, 20502 Malmo, Sweden, Department of Urology, Chang Gung Memorial Hospital, Tao-Yuan 33305, Taiwan, R.O.C., Department of Epidemiology, Karolinska Institutet, 171 77 Stockholm, Sweden, Department of Cell and Molecular Biology, Karolinska Institute, 171 77 Stockholm, Sweden, Regional Laboratories Region Skane, Clinical Pathology, 205 80 Malmo, Sweden, Department of Surgery (Urology), Memorial Sloan-Kettering Cancer Center, New York, NY 100 65, USA, Vancouver Prostate Centre and The Department of Urologic Sciences, University of British Columbia, Vancouver, BC Canada V6H 3Z6 and Tianjin Institute of Urology, Tianjin Medical University, Tianjin 300 211, China.

**RESUMEN / SUMMARY:** - The androgen receptor (AR) is a key regulator of prostate tumorigenesis through actions that are not fully understood. We identified the repressor element (RE)-1 silencing transcription factor (REST) as a mediator of AR actions on gene repression. Chromatin immunoprecipitation showed that AR binds chromatin regions containing well-characterized cis-elements known to mediate REST transcriptional repression, while cell imaging studies confirmed that REST and AR closely co-localize in vivo. Androgen-induced gene repression also involves modulation of REST protein turnover through actions on the ubiquitin ligase beta-TRCP. Androgen deprivation or AR blockage with inhibitor MDV3100 (Enzalutamide) leads to

neuroendocrine (NE) differentiation, a phenomenon that is mimicked by REST inactivation. Gene expression profiling revealed that REST not only acts to repress neuronal genes but also genes involved in cell cycle progression, including Aurora Kinase A, that has previously been implicated in the growth of NE-like castration-resistant tumors. The analysis of prostate cancer tissue microarrays revealed that tumors with reduced expression of REST have higher probability of early recurrence, independently of their Gleason score. The demonstration that REST modulates AR actions in prostate epithelia and that REST expression is negatively correlated with disease recurrence after prostatectomy, invite a deeper characterization of its role in prostate carcinogenesis.

[202]

**TÍTULO / TITLE:** - A DNA Methylation Prognostic Signature of Glioblastoma: Identification of NPTX2-PTEN-NF-kappaB Nexus.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Nov 15;73(22):6563-73. doi: 10.1158/0008-5472.CAN-13-0298. Epub 2013 Sep 27.

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

[0298](#)

**AUTORES / AUTHORS:** - Shukla S; Pia Patric IR; Thinagararjan S; Srinivasan S; Mondal B; Hegde AS; Chandramouli BA; Santosh V; Arivazhagan A; Somasundaram K

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Microbiology and Cell Biology, Indian Institute of Science; Sri SatyaSai Institute of Higher Medical Sciences; Departments of Neurosurgery and Neuropathology, National Institute of Mental Health and Neuro Sciences, Bangalore, India.

**RESUMEN / SUMMARY:** - Glioblastoma (GBM) is the most common, malignant adult primary tumor with dismal patient survival, yet the molecular determinants of patient survival are poorly characterized. Global methylation profile of GBM samples (our cohort; n = 44) using high-resolution methylation microarrays was carried out. Cox regression analysis identified a 9-gene methylation signature that predicted survival in GBM patients. A risk-score derived from methylation signature predicted survival in univariate analysis in our and The Cancer Genome Atlas (TCGA) cohort. Multivariate analysis identified methylation risk score as an independent survival predictor in TCGA cohort. Methylation risk score stratified the patients into low-risk and high-risk groups with significant survival difference. Network analysis revealed an activated NF-kappaB pathway association with high-risk group. NF-kappaB inhibition reversed glioma chemoresistance, and RNA interference studies identified interleukin-6 and intercellular adhesion molecule-1 as key NF-kappaB targets in imparting chemoresistance. Promoter hypermethylation of neuronal pentraxin II (NPTX2), a risky methylated gene, was confirmed by bisulfite sequencing in GBMs. GBMs and glioma cell lines had low levels of NPTX2 transcripts, which could be reversed upon methylation inhibitor treatment. NPTX2 overexpression induced apoptosis, inhibited proliferation and anchorage-independent growth, and rendered glioma cells chemosensitive. Furthermore, NPTX2 repressed NF-kappaB activity by inhibiting AKT through a p53-PTEN-dependent pathway, thus explaining the hypermethylation and downregulation of NPTX2 in NF-kappaB-activated high-risk GBMs. Taken together, a 9-gene methylation signature was identified as an independent GBM prognosticator and could be used for

GBM risk stratification. Prosurvival NF-kappaB pathway activation characterized high-risk patients with poor prognosis, indicating it to be a therapeutic target. Cancer Res; 73(22); 6563-73. ©2013 AACR.

[203]

**TÍTULO / TITLE:** - Cytotoxic activity of the casein kinase 2 inhibitor CX-4945 against T-cell acute lymphoblastic leukemia: targeting the unfolded protein response signaling.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Nov 20. doi: 10.1038/leu.2013.349.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.349](#)

**AUTORES / AUTHORS:** - Buontempo F; Orsini E; Martins LR; Antunes I; Lonetti A; Chiarini F; Tabellini G; Evangelisti C; Evangelisti C; Melchionda F; Pession A; Bertaina A; Locatelli F; McCubrey JA; Cappellini A; Barata JT; Martelli AM

**INSTITUCIÓN / INSTITUTION:** - Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy.

**RESUMEN / SUMMARY:** - Constitutively active casein kinase 2 (CK2) signaling is a common feature of T-cell acute lymphoblastic leukemia (T-ALL). CK2 phosphorylates PTEN tumor suppressor, resulting in PTEN stabilization and functional inactivation. Down-regulation of PTEN activity impacts on PI3K/Akt/mTOR signaling, which is of fundamental importance for T-ALL cell survival. These observations lend compelling weight to the application of CK2 inhibitors in the therapy of T-ALL. Here, we have analyzed the therapeutic potential of CX-4945, a novel, highly specific, orally available, ATP-competitive inhibitor of CK2 $\alpha$ . We show that CX-4945 treatment induced apoptosis in T-ALL cell lines and patient T-lymphoblasts. CX-4945 down-regulated PI3K/Akt/mTOR signaling in leukemic cells. Notably, CX-4945 affected the unfolded protein response (UPR), as demonstrated by a significant decrease in the levels of the main UPR regulator GRP78/BIP, and led to apoptosis via up-regulation of the ER stress/UPR cell death mediators IRE1 $\alpha$  and CHOP. In vivo administration of CX-4945 to a subcutaneous xenotransplant model of human T-ALL significantly delayed tumor growth. Our findings indicate that modulation of the ER stress/UPR signaling through CK2 inhibition could be exploited for inducing apoptosis in T-ALL cells and that CX-4945 may be an efficient treatment for those T-ALLs displaying up-regulation of CK2 $\alpha$ /PI3K/Akt/mTOR signaling. Leukemia accepted article preview online, 20 November 2013. doi:10.1038/leu.2013.349.

[204]

**TÍTULO / TITLE:** - The economic impact of cytoreductive surgery and tyrosine kinase inhibitor therapy in the treatment of advanced gastrointestinal stromal tumours: A Markov chain decision analysis.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Nov 8. pii: S0959-8049(13)00908-8. doi: 10.1016/j.ejca.2013.08.026.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.08.026](#)

**AUTORES / AUTHORS:** - Look Hong NJ; Chang SL; Raut CP

**INSTITUCIÓN / INSTITUTION:** - Division of Surgical Oncology, Brigham and Women's Hospital, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute,

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**RESUMEN / SUMMARY:** - PURPOSE: The current first-line treatment for patients with recurrent or metastatic gastrointestinal stromal tumours (GIST) is management with tyrosine kinase inhibition (TKI). There is an undefined role for surgery in the management of these patients. This study uses a cost analysis to examine the economic impact of treating patients with TKI in combination with surgery at different time-points in their treatment trajectories. METHODS: A Markov chain decision analysis was modelled over a 2-year time horizon to determine costs associated with surgery in combination with imatinib mesylate (IM) or sunitinib malate (SU) in seven scenarios varied by TKI agent, dose and disease status (stable versus localised progressive disease). Rates of disease progression, surgical morbidity, mortality and adverse drug reactions were extracted from the existing literature. Deterministic sensitivity analyses were performed to examine changes in cost due to variations in key variables. RESULTS: The least-costly scenario was to perform no surgery. The most costly scenario was to perform surgery on patients with localised progressive disease on IM 800mg. The overall range of costs clustered within approximately \$47,000 (USD). Variations in surgical cost, surgical mortality and cost of IM demonstrated thresholds for changing the least-costly scenario within plausible tested ranges. CONCLUSION: Costs of surgical intervention at different time-points within the treatment course of patients with advanced GIST fluctuate within a relatively narrow range, suggesting that costs arise primarily from the administration of TKI. The decision to pursue cytoreductive surgery should not be based on cost alone. Future studies should incorporate health-state utilities when available.

[205]

**TÍTULO / TITLE:** - Gut Peptide Profile and Chemotherapy-associated Dyspepsia Syndrome in Patients with Breast Cancer Undergoing FEC60 Chemotherapy.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):4951-7.

**AUTORES / AUTHORS:** - Riezzo G; Clemente C; Linsalata M; D'Attoma B; Orlando A; Campanella G; Giotta F; Russo F

**INSTITUCIÓN / INSTITUTION:** - Laboratorio di Fisiopatologia della Nutrizione, I.R.C.C.S. Saverio De Bellis, via Turi 27, 70013 Castellana Grotte, Bari, Italy.

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**RESUMEN / SUMMARY:** - Aim: The association of motilin, ghrelin, leptin, gastrin, pepsinogen (PG) I and II with cancer chemotherapy-associated dyspepsia syndrome (CADS) was investigated in 35 patients with breast cancer receiving first cycle of 5-fluorouracil, cyclophosphamide, epirubicin (FEC60) chemotherapy. PATIENTS AND METHODS: The onset of dyspeptic symptoms on days 3 and 10 after chemotherapy identified patients with and without CADS. Gastrointestinal symptoms were scored with the Gastrointestinal Symptom Scoring Rate (GSRs) questionnaire. Gastrointestinal peptides were evaluated by enzyme-linked immunosorbent assay. RESULTS: Twenty-one patients (60%) had CADS. The area under the curve (AUC) of ghrelin was higher, whereas that of PGI, PGII and motilin were lower in patients with CADS compared to those without. In patients with CADS, the AUC of PGI and PGII negatively correlated with the GSRs indigestion cluster. CONCLUSION: Impairment of gastrointestinal

motility suggested by low motilin concentrations and mucosal damage mirrored by an increase of ghrelin seem to be involved in the onset of CADS in patients during chemotherapy for breast cancer.

[206]

**TÍTULO / TITLE:** - Phosphatidylethanolamine-binding protein 4 is associated with breast cancer metastasis through Src-mediated Akt tyrosine phosphorylation.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Nov 25. doi: 10.1038/onc.2013.408.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.408](#)

**AUTORES / AUTHORS:** - Li H; Huang F; Fan L; Jiang Y; Wang X; Li J; Wang Q; Pan H; Sun J; Cao X; Wang X

**INSTITUCIÓN / INSTITUTION:** - Institute of Immunology, School of Medicine, Zhejiang University, Hangzhou, PR China.

**RESUMEN / SUMMARY:** - Metastasis is responsible for more than 90% of the mortality observed among patients with breast cancer. Human phosphatidylethanolamine-binding protein 4 (hPEBP4) is a novel member of the PEBP family and functions as an anti-apoptotic molecule. Here, we found that the metastatic MDA-MB-231 breast cancer cells expressed much higher levels of hPEBP4 than the nonmetastatic MCF-7 breast cancer cells and that the expression levels of hPEBP4 were positively correlated with the metastasis of clinical breast cancer. The hPEBP4 overexpression in the MDA-MB-231 cells significantly promoted cell invasion in vitro and increased the development of lymph node metastasis in vivo. Conversely, the silencing of hPEBP4 suppressed the cell-invasive ability both in vitro and in vivo. Further investigation showed that hPEBP4 promoted the expression or activity of the metastasis-related proteinases MMP (matrix metalloproteinase) 2, MMP9 and MMP13. This hPEBP4-potentiated cell invasion and MMP expression is due to an increase in Akt activation. Knockdown of Akt restored hPEBP4-induced breast tumor metastasis in the hPEBP4-MDA-MB-231 xenograft mouse model. Moreover, we found that hPEBP4 functioned as a scaffolding molecule and enhanced the association of Akt with Src to promote Akt tyrosine phosphorylation, a prerequisite for the full activation of Akt, in a phosphatidylethanolamine-binding domain-dependent manner. Given the present information about human breast cancer, these functional data from cell culture and animal studies suggest that, in human breast cancer hPEBP4 is a novel and clinically relevant metastasis accelerator gene and may be a new diagnostic marker and therapeutic target for breast cancer metastasis. Oncogene advance online publication, 25 November 2013; doi:10.1038/onc.2013.408.

[207]

**TÍTULO / TITLE:** - Elevated plasma fibrinogen levels are associated with a poor prognosis in patients with hepatocellular carcinoma.

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

**REVISTA / JOURNAL:** - Oncology. 2013;85(5):269-77. doi: 10.1159/000355502. Epub 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1159/000355502](#)

**AUTORES / AUTHORS:** - Kinoshita A; Onoda H; Imai N; Iwaku A; Oishi M; Tanaka K; Fushiya N; Koike K; Nishino H; Matsushima M; Tajiri H

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology and Hepatology, The Jikei University Daisan Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** - Objectives: Elevated plasma fibrinogen levels are associated with tumor progression and poor outcomes in cancer patients. We investigated the prognostic value of pretreatment plasma fibrinogen levels in patients with hepatocellular carcinoma (HCC). Methods: One hundred and thirteen patients with newly diagnosed HCC were retrospectively evaluated. We investigated the correlation between pretreatment plasma fibrinogen levels, clinicopathological parameters and overall survival. Both univariate and multivariate analyses were performed to identify the clinicopathological parameters associated with overall survival. Results: The median value of the pretreatment plasma fibrinogen level was 279 mg/dl. Elevated plasma fibrinogen levels were associated with larger tumor size, the presence of vascular invasion and higher Cancer Liver Italian Program scores. Lower plasma fibrinogen levels were associated with higher Child-Pugh grades. The overall survival rates in patients with pretreatment plasma fibrinogen levels  $\geq 315$  mg/dl were significantly lower than those with a pretreatment plasma fibrinogen level  $< 315$  mg/dl ( $p = 0.016$ ). On multivariate analysis, the plasma fibrinogen levels (per 100 mg/dl) were found to be independently associated with overall survival (hazard ratio 1.236;  $p = 0.046$ ). Conclusions: This study demonstrates that elevated pretreatment plasma fibrinogen levels are associated with tumor progression and are independently associated with a poor prognosis in patients with HCC. © 2013 S. Karger AG, Basel.

[208]

**TÍTULO / TITLE:** - Quantification of expression of antigens targeted by antibody-based therapy in chronic lymphocytic leukemia.

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

**REVISTA / JOURNAL:** - Am J Clin Pathol. 2013 Dec;140(6):813-8. doi: 10.1309/AJCPYFQ4XMGJD6TI.

●● [Enlace al texto completo \(gratis o de pago\) 1309/AJCPYFQ4XMGJD6TI](#)

**AUTORES / AUTHORS:** - Tembhare PR; Marti G; Wiestner A; Degheidy H; Farooqui M; Kreitman RJ; Jasper GA; Yuan CM; Liewehr D; Venzon D; Stetler-Stevenson M

**INSTITUCIÓN / INSTITUTION:** - Flow Cytometry Unit, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Dr, Bethesda, MD, 20892; [stetler@mail.nih.gov](mailto:stetler@mail.nih.gov).

**RESUMEN / SUMMARY:** - Objectives Anti-CD20 (rituximab), anti-CD52 (alemtuzumab), anti-CD22 (BL22, HA22), and anti-CD25 (Oncotac) are therapeutic options that are the mainstay or in preclinical development for the treatment of chronic lymphocytic leukemia (CLL). Studies suggest that levels of surface antigen expression may affect response to monoclonal antibody-based therapy. Methods Using the flow cytometric Quantibrite method (BD Biosciences, San Jose, CA) to determine antibodies bound per cell, we quantified the levels of surface expression of CD20, CD22, CD25, and CD52 in CLL cells from 28 untreated patients. Results The CLL cells in all cases expressed CD20, CD22, and CD52 but 4 (14%) cases were negative for CD25. Although the ranking of levels of expression from highest to lowest was CD52, CD20, CD22, and CD25, the level of antigen expression on any specific case could not be accurately

predicted. Conclusions Quantification of antigens might be useful in evaluating new antigens to target for therapy and may provide a systematic approach to selecting individualized therapy in CLL.

[209]

**TÍTULO / TITLE:** - Structural Basis for Eliciting a Cytotoxic Effect in HER2-Overexpressing Cancer Cells via Binding to the Extracellular Domain of HER2.

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

**REVISTA / JOURNAL:** - Structure. 2013 Nov 5;21(11):1979-91. doi: 10.1016/j.str.2013.08.020. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [1016/j.str.2013.08.020](#)

**AUTORES / AUTHORS:** - Jost C; Schilling J; Tamaskovic R; Schwill M; Honegger A; Pluckthun A

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, University of Zurich, 8057 Zurich, Switzerland.

**RESUMEN / SUMMARY:** - Human epidermal growth factor receptor-2 (HER2) is a receptor tyrosine kinase directly linked to the growth of malignancies from various origins and a validated target for monoclonal antibodies and kinase inhibitors. Utilizing a new approach with designed ankyrin repeat proteins (DARPs) as alternative binders, we show that binding of two DARPs connected by a short linker, one targeting extracellular subdomain I and the other subdomain IV, causes much stronger cytotoxic effects on the HER2-addicted breast cancer cell line BT474, surpassing the therapeutic antibody trastuzumab. We determined crystal structures of these DARPs in complex with the respective subdomains. Detailed models of the full-length receptor, constrained by its rigid domain structures and its membrane anchoring, explain how the bispecific DARPs connect two membrane-bound HER2 molecules, distorting them such that they cannot form signaling-competent dimers with any EGFR family member, preventing any kinase dimerization, and thus leading to a complete loss of signaling.

[210]

**TÍTULO / TITLE:** - Inhibition of c-Src blocks oestrogen-induced apoptosis and restores oestrogen-stimulated growth in long-term oestrogen-deprived breast cancer cells.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Oct 30. pii: S0959-8049(13)00901-5. doi: 10.1016/j.ejca.2013.10.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.10.001](#)

**AUTORES / AUTHORS:** - Fan P; Agboke FA; McDaniel RE; Sweeney EE; Zou X; Creswell K; Jordan VC

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC 20057, USA.

**RESUMEN / SUMMARY:** - PURPOSE: Our publications demonstrate that physiological concentrations of oestrogen (E2) induce endoplasmic reticulum and oxidative stress which finally result in apoptosis in E2-deprived breast cancer cells, MCF-7:5C. c-Src is involved in the process of E2-induced stress. To mimic the clinical administration of c-Src inhibitors, we treated cells with either E2, a c-Src inhibitor PP2, or the combination

for 8 weeks to further explore the apoptotic potential of the c-Src inhibitor and E2 on MCF-7:5C cells. METHODS: Protein levels of receptors and signalling pathways were examined by immunoblotting. Expression of mRNA was detected through real-time polymerase chain reaction (PCR). Cell cycles were analysed by flow cytometry. RESULTS: Long-term treatment with PP2 alone or E2 alone decreased cell growth. In contrast, a combination of PP2 and E2 blocked apoptosis and the resulting cell line (MCF-7:PF) was unique, as they grew vigorously in culture with physiological levels of E2, which could be blocked by the pure antioestrogen ICI182,780. One major change was that PP2 collaborated with E2 to increase the level of insulin-like growth factor-1 receptor beta (IGF-1Rbeta). Blockade of IGF-1Rbeta completely abolished E2-stimulated growth in MCF-7:PF cells. Furthermore, combination treatment up-regulated transcription factors, Twist1 and Snail, and repressed E-cadherin expression which made MCF-7:PF cells display a characteristic phenotype of epithelial-mesenchymal transition (EMT). CONCLUSIONS: These data illustrate the role of the c-Src inhibitor to block E2-induced apoptosis and enhance E2-stimulated growth. Caution must be exercised when considering c-Src inhibitors in clinical trials following the development of acquired resistance to aromatase inhibitors, especially in the presence of the patient's own oestrogen.

[211]

**TÍTULO / TITLE:** - Tonic Activation of Bax Primes Neural Progenitors for Rapid Apoptosis through a Mechanism Preserved in Medulloblastoma.

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

**REVISTA / JOURNAL:** - J Neurosci. 2013 Nov 13;33(46):18098-108. doi: 10.1523/JNEUROSCI.2602-13.2013.

●● [Enlace al texto completo \(gratis o de pago\) 1523/JNEUROSCI.2602-13.2013](#)

**AUTORES / AUTHORS:** - Crowther AJ; Gama V; Bevilacqua A; Chang SX; Yuan H; Deshmukh M; Gershon TR

**INSTITUCIÓN / INSTITUTION:** - Departments of Neurology, Radiation Oncology, and Radiology, Neuroscience Center, Lineberger Comprehensive Cancer Center, and Department of Cell Biology and Physiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599.

**RESUMEN / SUMMARY:** - Commitment to survival or apoptosis within expanding progenitor populations poses distinct risks and benefits to the organism. We investigated whether specialized mechanisms regulate apoptosis in mouse neural progenitors and in the progenitor-derived brain tumor medulloblastoma. Here, we identified constitutive activation of proapoptotic Bax, maintained in check by Bcl-xL, as a mechanism for rapid cell death, common to postnatal neural progenitors and medulloblastoma. We found that tonic activation of Bax in cerebellar progenitors, along with sensitivity to DNA damage, was linked to differentiation state. In cerebellar progenitors, active Bax localized to mitochondria, where it was bound to Bcl-xL. Disruption of Bax:Bcl-xL binding by BH3-mimetic ABT 737 caused rapid apoptosis of cerebellar progenitors and primary murine medulloblastoma cells. Conditional deletion of Mcl-1, in contrast, did not cause death of cerebellar progenitors. Our findings identify a mechanism for the sensitivity of brain progenitors to typical anticancer therapies and

reveal that this mechanism persists in medulloblastoma, a malignant brain tumor markedly sensitive to radiation and chemotherapy.

[212]

**TÍTULO / TITLE:** - Proteasome inhibition with bortezomib induces cell death in GBM stem-like cells and temozolomide-resistant glioma cell lines, but stimulates GBM stem-like cells' VEGF production and angiogenesis.

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

**REVISTA / JOURNAL:** - J Neurosurg. 2013 Dec;119(6):1415-23. doi: 10.3171/2013.7.JNS1323. Epub 2013 Oct 4.

●● [Enlace al texto completo \(gratis o de pago\) 3171/2013.7.JNS1323](#)

**AUTORES / AUTHORS:** - Bota DA; Alexandru D; Keir ST; Bigner D; Vredenburgh J; Friedman HS

**INSTITUCIÓN / INSTITUTION:** - Departments of Neurology and.

**RESUMEN / SUMMARY:** - Object Recurrent malignant gliomas have inherent resistance to traditional chemotherapy. Novel therapies target specific molecular mechanisms involved in abnormal signaling and resistance to apoptosis. The proteasome is a key regulator of multiple cellular functions, and its inhibition in malignant astrocytic lines causes cell growth arrest and apoptotic cell death. The proteasome inhibitor bortezomib was reported to have very good in vitro activity against malignant glioma cell lines, with modest activity in animal models as well as in clinical trials as a single agent. In this paper, the authors describe the multiple effects of bortezomib in both in vitro and in vivo glioma models and offer a novel explanation for its seeming lack of activity. Methods Glioma stem-like cells (GSCs) were obtained from resected glioblastomas (GBMs) at surgery and expanded in culture. Stable glioma cell lines (U21 and D54) as well as temozolomide (TMZ)-resistant glioma cells derived from U251 and D54-MG were also cultured. GSCs from 2 different tumors, as well as D54 and U251 cells, were treated with bortezomib, and the effect of the drug was measured using an XTT cell viability assay. The activity of bortezomib was then determined in D54-MG and/or U251 cells using apoptosis analysis as well as caspase-3 activity and proteasome activity measurements. Human glioma xenograft models were created in nude mice by subcutaneous injection. Bevacizumab was administered via intraperitoneal injection at a dose of 5 mg/kg daily. Bortezomib was administered by intraperitoneal injection 1 hour after bevacizumab administration in doses of at a dose of 0.35 mg/kg on days 1, 4, 8, and 11 every 21 days. Tumors were measured twice weekly. Results Bortezomib induced caspase-3 activation and apoptotic cell death in stable glioma cell lines and in glioma stem-like cells (GSCs) derived from malignant tumor specimens Furthermore, TMZ-resistant glioma cell lines retained susceptibility to the proteasome inhibition. The bortezomib activity was directly proportional with the cells' baseline proteasome activity. The proteasome inhibition stimulated both hypoxia-inducible factor (HIF)-1alpha and vascular endothelial growth factor (VEGF) production in malignant GSCs. As such, the VEGF produced by GSCs stimulated endothelial cell growth, an effect that could be prevented by the addition of bevacizumab (VEGF antibody) to the media. Similarly, administration of bortezomib and bevacizumab to athymic mice carrying subcutaneous malignant glioma xenografts resulted in greater tumor inhibition and greater improvement in survival than administration of either drug alone. These data indicate that simultaneous proteasome inhibition and VEGF

blockade offer increased benefit as a strategy for malignant glioma therapy.  
Conclusions The results of this study indicate that combination therapies based on bortezomib and bevacizumab might offer an increased benefit when the two agents are used in combination. These drugs have a complementary mechanism of action and therefore can be used together to treat TMZ-resistant malignant gliomas.

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[213]

**TÍTULO / TITLE:** - A gene signature of bone metastatic colonization sensitizes for tumor-induced osteolysis and predicts survival in lung cancer.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Oct 28. doi: 10.1038/onc.2013.440.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.440](#)

**AUTORES / AUTHORS:** - Luis-Ravelo D; Anton I; Zanduetta C; Valencia K; Ormazabal C; Martinez-Canarias S; Guruceaga E; Perurena N; Vicent S; De Las Rivas J; Lecanda F

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology, Adhesion and Metastasis Laboratory, University of Navarra, Pamplona, España.

**RESUMEN / SUMMARY:** - Bone metastasis of lung adenocarcinoma (AC) is a frequent complication of advanced disease. The purpose of this study was to identify key mediators conferring robust prometastatic activity with clinical significance. We isolated highly metastatic subpopulations (HMS) using a previously described in vivo model of lung AC bone metastasis. We performed transcriptomic profiling of HMS and stringent bioinformatics filtering. Functional validation was assessed by overexpression and lentiviral silencing of single, double and triple combination in vivo and in vitro. We identified HDAC4, PITX1 and ROBO1 that decreased bone metastatic ability after their simultaneous abrogation. These effects were solely linked to defects in osseous colonization. The molecular mechanisms related to bone colonization were mediated by non-cell autonomous effects that include the following: (1) a marked decrease in osteoclastogenic activity in vitro and in vivo, an effect associated with reduced pro-osteoclastogenic cytokines IL-11 and PTHrP expression levels, as well as decreased in vitro expression of stromal rankl in conditions mimicking tumor-stromal interactions; (2) an abrogated response to TGF-beta signaling by decreased phosphorylation and levels of Smad2/3 in tumor cells and (3) an impaired metalloproteolytic activity in vitro. Interestingly, coexpression of HDAC4 and PITX1 conferred high prometastatic activity in vivo. Further, levels of both genes correlated with patients at higher risk of metastasis in a clinical lung AC data set and with a poorer clinical outcome. These findings provide functional and clinical evidence that this metastatic subset is an important determinant of osseous colonization. These data suggest novel therapeutic targets to effectively block lung AC bone metastasis. Oncogene advance online publication, 28 October 2013; doi:10.1038/onc.2013.440.

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[214]

**TÍTULO / TITLE:** - microRNA-18a induces apoptosis in colon cancer cells via the autophagolysosomal degradation of oncogenic heterogeneous nuclear ribonucleoprotein A1.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Oct 28. doi: 10.1038/onc.2013.429.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.429](https://doi.org/10.1038/onc.2013.429)

**AUTORES / AUTHORS:** - Fujiya M; Konishi H; Mohamed Kamel MK; Ueno N; Inaba Y; Moriichi K; Tanabe H; Ikuta K; Ohtake T; Kohgo Y

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical College, Asahikawa, Japan.

**RESUMEN / SUMMARY:** - It is well known that microRNAs (miRs) are abnormally expressed in various cancers and target the messenger RNAs (mRNAs) of cancer-associated genes. While (miRs) are abnormally expressed in various cancers, whether miRs directly target oncogenic proteins is unknown. The present study investigated the inhibitory effects of miR-18a on colon cancer progression, which was considered to be mediated through its direct binding and degradation of heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1). An MTT assay and xenograft model demonstrated that the transfection of miR-18a induced apoptosis in SW620 cells. A binding assay revealed direct binding between miR-18a and hnRNP A1 in the cytoplasm of SW620 cells, which inhibited the oncogenic functions of hnRNP A1. A competitor RNA, which included the complementary sequence of the region of the miR-18a-hnRNP A1 binding site, repressed the effects of miR-18a on the induction of cancer cell apoptosis. In vitro single and in vivo double isotope assays demonstrated that miR-18a induced the degradation of hnRNP A1. An immunocytochemical study of hnRNP A1 and LC3-II and the inhibition of autophagy by 3-methyladenine and ATG7, p62 and BAG3 siRNA showed that miR-18a and hnRNP A1 formed a complex that was degraded through the autophagolysosomal pathway. This is the first report showing a novel function of a miR in the autophagolysosomal degradation of an oncogenic protein resulting from the creation of a complex consisting of the miR and a RNA-binding protein, which suppressed cancer progression. Oncogene advance online publication, 28 October 2013; doi:10.1038/onc.2013.429.

[215]

**TÍTULO / TITLE:** - Novel mechanism of MDA-7/IL-24 cancer-specific apoptosis through SARI induction.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-1062](https://doi.org/10.1158/0008-5472.CAN-13-1062)

**AUTORES / AUTHORS:** - Dash R; Bhoopathi P; Das SK; Sarkar S; Emdad L; Dasgupta S; Sarkar D; Fisher PB

**INSTITUCIÓN / INSTITUTION:** - Institute of Life Sciences.

**RESUMEN / SUMMARY:** - Subtraction-hybridization combined with induction of cancer cell terminal differentiation in human melanoma cells identified melanoma differentiation associated gene-7 (mda-7/IL-24) and SARI (Suppressor of AP-1, induced by IFN) that display potent antitumor activity. These genes are not constitutively expressed in cancer cells and forced expression of mda-7/IL-24 (Ad.mda-7) or SARI (Ad.SARI) promotes cancer-specific cell death. Ectopic expression of mda-7/IL-24 induces SARI mRNA and protein in a panel of different cancer cells leading to cell death, without harming corresponding normal cells. Simultaneous inhibition of K-ras downstream extracellular regulated kinase 1/2 (ERK1/2) signaling in pancreatic

cancer cells reverses the translational block of MDA-7/IL-24 and induces SARI expression and cell death. Using SARI-antisense-based approaches we demonstrate that SARI expression is necessary for mda-7/IL-24 antitumor effects. Secreted MDA-7/IL-24 protein induces antitumor 'bystander' effects by promoting its own expression. Recombinant MDA-7/IL-24 (His-MDA-7) induces SARI expression, supporting the involvement of SARI in the MDA-7/IL-24-driven autocrine loop culminating in antitumor effects. Moreover, His-MDA-7 after binding to its cognate receptors (IL-20R1/IL-20R2 or IL-22R/IL-20R2) induces intracellular signaling by phosphorylation of p38 MAPK leading to transcription of a family of growth arrest and DNA damage inducible (GADD) genes, culminating in apoptosis. Inhibition of p38 MAPK fails to induce SARI following Ad.mda-7 infection. These findings reveal the significance of the mda-7/IL-24-SARI axis in cancer-specific killing, and provide a potential strategy for treating both local and metastatic disease.

[216]

**TÍTULO / TITLE:** - Tolfenamic acid induces apoptosis and growth inhibition in anaplastic thyroid cancer: Involvement of nonsteroidal anti-inflammatory drug-activated gene-1 expression and intracellular reactive oxygen species generation.

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

**REVISTA / JOURNAL:** - Free Radic Biol Med. 2013 Nov 8;67C:115-130. doi: 10.1016/j.freeradbiomed.2013.10.818.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1016/j.freeradbiomed.2013.10.818](#)

**AUTORES / AUTHORS:** - Chang JW; Kang SU; Choi JW; Shin YS; Baek SJ; Lee SH; Kim CH

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology, School of Medicine, Ajou University, Suwon 442-749, Korea; Center for Cell Death-Regulating Biodrugs, School of Medicine, Ajou University, Suwon 442-749, Korea.

**RESUMEN / SUMMARY:** - Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used for the treatment of inflammatory diseases. However, certain NSAIDs also have antitumor activities in various cancers, including head and neck cancer, through cyclooxygenase-dependent or independent pathways. Nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1), a TGF-beta superfamily protein, is induced by NSAIDs and has been shown to be induced by several antitumorigenic compounds and to exhibit proapoptotic and antitumorigenic activities. In this report, we demonstrate for the first time that tolfenamic acid (TA) transcriptionally induced the expression of NAG-1 during TA-induced apoptosis of anaplastic thyroid cancer (ATC) cells. TA reduced the viability of ATC cells in a dose-dependent manner and induced apoptosis, findings that were coincident with NAG-1 expression. Overexpression of the NAG-1 gene using cDNA enhanced the apoptotic effect of TA, whereas suppression of NAG-1 expression by small interfering RNA attenuated TA-induced apoptosis. Subsequently, we found that intracellular ROS generation plays an important role in activating the proapoptotic protein NAG-1. Then, we confirmed antitumorigenic effects of TA in a nude mouse orthotopic ATC model, and this result accompanied the augmentation of NAG-1 expression and ROS generation in tumor tissue. Taken together, these results demonstrate that TA induces apoptosis via NAG-1 expression and ROS generation in

in vitro and in vivo ATC models, providing a novel mechanistic explanation and indicating a potential chemotherapeutic approach for treatment of ATC.

[217]

**TÍTULO / TITLE:** - Current Status of Targeted Therapy for Anaplastic Lymphoma Kinase-Rearranged Non-Small Cell Lung Cancer.

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

**REVISTA / JOURNAL:** - Clin Pharmacol Ther. 2013 Oct 3. doi: 10.1038/clpt.2013.200.

●● Enlace al texto completo (gratis o de pago) [1038/clpt.2013.200](#)

**AUTORES / AUTHORS:** - Solomon B; Wilner KD; Shaw AT

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne, Australia [2] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia.

**RESUMEN / SUMMARY:** - The identification of chromosomal rearrangements involving the anaplastic lymphoma kinase (ALK) gene in ~3-5% of non-small cell lung cancer (NSCLC) tissues and the demonstration that the first-in-class ALK tyrosine kinase inhibitor, crizotinib, can effectively target these tumors represent a significant advance in the evolution of personalized medicine for NSCLC. Single-arm studies demonstrating rapid and durable responses in the majority of ALK-positive NSCLC patients treated with crizotinib have been followed by a randomized phase III clinical trial in which superiority of crizotinib over chemotherapy was seen in previously treated ALK-positive NSCLC patients. However, despite the initial responses, most patients develop acquired resistance to crizotinib. Several novel therapeutic approaches targeting ALK-positive NSCLC are currently under evaluation in clinical trials, including second-generation ALK inhibitors, such as LDK378, CH5424802 (RO5424802802), and AP26113, and heat shock protein 90 inhibitors. Clinical Pharmacology & Therapeutics (2013); advance online publication 13 November 2013. doi:10.1038/clpt.2013.200.

[218]

**TÍTULO / TITLE:** - Germline and Somatic Mutations in Homologous Recombination Genes Predict Platinum Response and Survival in Ovarian, Fallopian Tube, and Peritoneal Carcinomas.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-](#)

[2287](#)

**AUTORES / AUTHORS:** - Pennington KP; Walsh T; Harrell MI; Lee MK; Pennil C; Rendi M; Thornton A; Norquist BM; Casadei S; Nord A; Agnew KJ; Pritchard CC; Scroggins S; Garcia RL; King MC; Swisher EM

**INSTITUCIÓN / INSTITUTION:** - Obstetrics and Gynecology, University of Washington Medical Center.

**RESUMEN / SUMMARY:** - PURPOSE: Hallmarks of germline BRCA1/2-associated ovarian carcinomas include chemosensitivity and improved survival. The therapeutic impact of somatic BRCA1/2 mutations and mutations in other homologous recombination (HR) DNA repair genes is uncertain. EXPERIMENTAL DESIGN: Using targeted capture and massively parallel genomic sequencing, we assessed 390

ovarian carcinomas for germline and somatic loss-of-function mutations in 30 genes, including BRCA1, BRCA2, and 11 other genes in the HR pathway. RESULTS: 31% of ovarian carcinomas had a deleterious germline (24%) and/or somatic (9%) mutation in one or more of the 13 HR genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAD51D. Non-serous ovarian carcinomas had similar rates of HR mutations to serous carcinomas (28% vs. 31%,  $p=0.6$ ), including clear cell, endometrioid, and carcinosarcoma. The presence of germline and somatic HR mutations was highly predictive of primary platinum sensitivity ( $p=0.0002$ ) and improved overall survival ( $p=0.0006$ ), with median overall survival 66 months in germline HR mutation carriers, 59 months in cases with a somatic HR mutation, and 41 months for cases without an HR mutation. CONCLUSIONS: Germline or somatic mutations in HR genes are present in almost one-third of ovarian carcinomas, including both serous and non-serous histologies. Somatic BRCA1/2 mutations and mutations in other HR genes have a similar positive impact on overall survival and platinum responsiveness as germline BRCA1/2 mutations. The similar rate of HR mutations in non-serous carcinomas supports their inclusion in PARP inhibitor clinical trials.

[219]

**TÍTULO / TITLE:** - Targeted induction of apoptosis in glioblastoma multiforme cells by an MRP3-specific TRAIL fusion protein in vitro.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1155-7](#)

**AUTORES / AUTHORS:** - Wang LH; Ni CW; Lin YZ; Yin L; Jiang CB; Lv CT; Le Y; Lang Y; Zhao CY; Yang K; Jiao BH; Yin J

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Second Military Medical University, Xiangyin Road No. 800, Shanghai, 200433, China.

**RESUMEN / SUMMARY:** - Single-chain Fv fragments (scFvs) consist of the variable heavy-chain (VH) and variable light-chain (VL) domains, which are the smallest immunoglobulin fragments containing the whole antigen-binding site. Human soluble tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) proves to acquire a potent pro-apoptotic activity only after selective binding to a predefined tumor cell surface antigen and has no off-target effects towards normal cells. Glioblastoma multiforme (GBM) is the most frequent and aggressive type of brain tumor and overexpresses human multidrug resistance protein 3 (MRP3). In this study, we designed a novel fusion protein, termed scFvM58-sTRAIL, in which the MRP3-specific scFv antibody M58 was genetically fused to the N-terminus of human soluble TRAIL (sTRAIL). The recombinant scFvM58-sTRAIL fusion protein, expressed in *Escherichia coli*, was purified by chromatography and tested for cytotoxicity. scFvM58-sTRAIL showed a significant apoptosis-inducing activity towards MRP3-positive GBM cells in vitro. The pro-apoptotic activity of scFvM58-sTRAIL towards GBM cells was strongly inhibited in the presence of the parental scFvM58 antibody, suggesting that cytotoxic activity is MRP3-restricted. In a control experiment with MRP3-negative Jurkat cells, scFvM58-sTRAIL did not induce apparent apoptosis. In addition, through target antigen-restricted binding, scFvM58-sTRAIL was capable of activating not only TRAIL-R1 but also TRAIL-R2. In conclusion, our results suggest that fusion protein scFvM58-

sTRAIL with specificity for MRP3 is a highly selective therapeutic agent and may provide an alternative therapy for human GBM.

[220]

**TÍTULO / TITLE:** - Suppression of the death gene BIK is a critical factor for resistance to tamoxifen in MCF-7 breast cancer cells.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):1777-86. doi: 10.3892/ijo.2013.2127. Epub 2013 Oct 4.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.2127](#)

**AUTORES / AUTHORS:** - Viedma-Rodriguez R; Baiza-Gutman LA; Garcia-Carranca A; Moreno-Fierros L; Salamanca-Gomez F; Arenas-Aranda D

**INSTITUCIÓN / INSTITUTION:** - Unit of Medical Research in Human Genetics, Medical National Center, Century XXI, Mexican Institute of Social Insurance, Mexico City, Mexico.

**RESUMEN / SUMMARY:** - Apoptosis is controlled by the BCL-2 family of proteins, which can be divided into three different subclasses based on the conservation of BCL-2 homology domains. BIK is a founding member of the BH3-only pro-apoptotic protein family. BIK is predominantly localized in the endoplasmic reticulum (ER) and induces apoptosis through the mitochondrial pathway by mobilizing calcium from the ER to the mitochondria. In this study, we determined that suppression of the death gene Bik promotes resistance to tamoxifen (TAM) in MCF-7 breast cancer cells. We utilized small interfering (siRNA) to specifically knockdown BIK in MCF-7 cells and studied their response to tamoxifen. The levels of cell apoptosis, the potential mitochondrial membrane (Psim), and the activation of total caspases were analyzed. Western blot analysis was used to determine the expression of some BCL-2 family proteins. Flow cytometry studies revealed an increase in apoptosis level in MCF-7 cells and a 2-fold increase in relative BIK messenger RNA (mRNA) expression at a concentration of 6.0 μM of TAM. BIK silencing, with a specific RNAi, blocked TAM-induced apoptosis in 45±6.78% of cells. Moreover, it decreased mitochondrial membrane potential (Psim) and total caspase activity, and exhibited low expression of pro-apoptotic proteins BAX, BAK, PUMA and a high expression of BCL-2 and MCL-1. The above suggests resistance to TAM, regulating the intrinsic pathway and indicate that BIK comprises an important factor in the process of apoptosis, which may exert an influence the ER pathway, which regulates mitochondrial integrity. Collectively, our results show that BIK is a central component of the programmed cell death of TAM-induced MCF-7 breast cancer cells. The silencing of BIK gene will be useful for future studies to establish the mechanisms of regulation of resistance to TAM.

[221]

**TÍTULO / TITLE:** - The HSP90 Inhibitor Ganetespib Synergizes with the MET Kinase Inhibitor Crizotinib in both Crizotinib-Sensitive and -Resistant MET-Driven Tumor Models.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Dec 1;73(23):7022-33. doi: 10.1158/0008-5472.CAN-13-1156. Epub 2013 Oct 11.

- Enlace al texto completo (gratuito o de pago) [1158/0008-5472.CAN-13-1156](https://doi.org/10.1158/0008-5472.CAN-13-1156)

**AUTORES / AUTHORS:** - Miyajima N; Tsutsumi S; Sourbier C; Beebe K; Mollapour M; Rivas C; Yoshida S; Trepel JB; Huang Y; Tatokoro M; Shinohara N; Nonomura K; Neckers L

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Urologic Oncology Branch and Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland; Departments of Urology, Biochemistry, and Molecular Biology, Cancer Research Institute, SUNY Upstate Medical University, Syracuse, New York; and Department of Urology, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

**RESUMEN / SUMMARY:** - The proto-oncogene MET is aberrantly activated via overexpression or mutation in numerous cancers, making it a prime anticancer molecular target. However, the clinical success of MET-directed tyrosine kinase inhibitors (TKI) has been limited due, in part, to mutations in the MET kinase domain that confer therapeutic resistance. Circumventing this problem remains a key challenge to improving durable responses in patients receiving MET-targeted therapy. MET is an HSP90-dependent kinase, and in this report we show that HSP90 preferentially interacts with and stabilizes activated MET, regardless of whether the activation is ligand-dependent or is a consequence of kinase domain mutation. In contrast, many MET-TKI show a preference for the inactive form of the kinase, and activating mutations in MET can confer resistance. Combining the HSP90 inhibitor ganetespib with the MET-TKI crizotinib achieves synergistic inhibition of MET, its downstream signaling pathways, and tumor growth in both TKI-sensitive and -resistant MET-driven tumor models. These data suggest that inclusion of an HSP90 inhibitor can partially restore TKI sensitivity to previously resistant MET mutants, and they provide the foundation for clinical evaluation of this therapeutic combination in patients with MET-driven cancers. Cancer Res; 73(23); 7022-33. ©2013 AACR.

[222]

**TÍTULO / TITLE:** - Serum carbohydrate antigen 19-9 and prognosis of patients with gastric cancer.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 15.

- Enlace al texto completo (gratuito o de pago) [1007/s13277-013-1177-1](https://doi.org/10.1007/s13277-013-1177-1)

**AUTORES / AUTHORS:** - Xiao J; He X; Wang Z; Hu J; Sun F; Qi F; Yang S; Xiao Z

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Laboratory, People's Hospital of Ganzhou, Ganzhou, 341000, China.

**RESUMEN / SUMMARY:** - Previous studies have assessed the prognostic role of serum carbohydrate antigen 19-9 (CA 19-9) concentration in patients with gastric cancer, but the findings from those studies were inconsistent. We searched the PubMed and Web of Science databases to find eligible studies assessing the prognostic role of CA 19-9 in patients with gastric cancer. Twelve studies with a total of 5,072 gastric cancer patients were finally included into the meta-analysis. The pooled hazard ratio (HR) with corresponding 95 % confidence interval (95 % CI) for overall survival were calculated to assess the prognostic role of CA 19-9 in patients with gastric cancer. Overall, elevated serum concentration of CA 19-9 (>37 U/mL) was associated with poorer

overall survival in patients with gastric cancer (fixed-effects HR = 1.36, 95 % CI 1.24-1.48, P < 0.001). Subgroup analysis by study design further showed that elevated serum concentration of CA 19-9 was associated with poorer overall survival in patients with gastric cancer. There was no obvious risk of publication bias. Elevated concentration of serum CA 19-9 is associated with poorer overall survival in patients with gastric cancer.

[223]

**TÍTULO / TITLE:** - Molecular analysis of the BCR-ABL1 kinase domain in chronic-phase chronic myelogenous leukemia treated with tyrosine kinase inhibitors in practice: Study by the Nagasaki CML Study Group.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Nov 5. pii: S0145-2126(13)00380-9. doi: 10.1016/j.leukres.2013.10.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.10.022](#)

**AUTORES / AUTHORS:** - Itonaga H; Tsushima H; Imanishi D; Hata T; Doi Y; Mori S; Sasaki D; Hasegawa H; Matsuo E; Nakashima J; Kato T; Horai M; Taguchi M; Matsuo M; Taniguchi H; Makiyama J; Sato S; Horio K; Ando K; Moriwaki Y; Sawayama Y; Ogawa D; Yamasaki R; Takasaki Y; Imaizumi Y; Taguchi J; Kawaguchi Y; Yoshida S; Joh T; Moriuchi Y; Nonaka H; Soda H; Fukushima T; Nagai K; Kamihira S; Tomonaga M; Yanagihara K; Miyazaki Y

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Atomic Bomb Disease and Hibakusha Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki City, Nagasaki, Japan; Nagasaki CML Study Group, Nagasaki, Japan.

**RESUMEN / SUMMARY:** - An appropriate trigger for BCR-ABL1 mutation analysis has not yet been established in unselected cohorts of chronic-phase chronic myelogenous leukemia patients. We examined 92 patients after 12 months of tyrosine kinase inhibitor (TKI) treatment in Nagasaki Prefecture, Japan. Univariate analysis revealed that significant factors associated with not attaining a major molecular response (MMR) were the presence of the minor BCR-ABL1 fusion gene, a low daily dose of TKI, and the emergence of BCR-ABL1 kinase domain mutations conferring resistance to imatinib. Factors associated with the loss of sustained MMR were a low daily dose of TKI and the emergence of alternatively spliced BCR-ABL1 mRNA with a 35-nucleotide insertion. Taken together, our results suggest that the search for BCR-ABL1 mutations should be initiated if patients have not achieved MMR following 12 months of TKI treatment.

[224]

**TÍTULO / TITLE:** - Induction of apoptosis by VB1 in breast cancer cells: The role of reactive oxygen species and Bcl-2 family proteins.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Nov 26. doi: 10.3892/ijmm.2013.1567.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1567](#)

**AUTORES / AUTHORS:** - Liu LH; Zhou YJ; Ding L; Zhang SZ; Sun J; Cao JG

**INSTITUCIÓN / INSTITUTION:** - The First Hospital of Changsha, Changsha, Hunan 410005, P.R. China.

**RESUMEN / SUMMARY:** - We have previously reported that the EVn-50 mixture of vitexins (lignan compounds) containing the purified vitexin (neolignan) compound, 6-hydroxy-4(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, termed VB1, exhibits potent anticancer activity through the induction of apoptosis in several types of cancer cells, including MDA-MB231 cells. However, the exact molecular mechanisms by which VB1 induces apoptosis in MDA-MB231 cells have not yet been fully elucidated. In this study, to our knowledge, we provide for the first time mechanistic evidence that VB1-induced apoptosis in the human breast cancer line, MDA-MB-231, is associated with the generation of reactive oxygen species (ROS), the activation of caspases and the modulation of the expression of myeloid leukemia cell differentiation protein 1 (Mcl1), B cell lymphoma2 (Bcl-2) and Bcl-2-associated X (Bax) proteins. The silencing of Mcl-1 by RNA interference enhanced VB1-induced apoptosis. In addition, VB1 did not induce ROS generation or apoptosis in the immortalized noncancerous breast cell line, MCF-10A. Our findings reveal a novel mechanism underlying VB1-induced apoptosis, and highlight VB1 as a promising candidate for the therapy of human breast cancer.

[225]

**TÍTULO / TITLE:** - Differences in RRM1 protein expression between diagnostic biopsies and resection specimens, and changes during carboplatin and paclitaxel treatment, in non-small-cell lung cancer.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Aug 26. doi: 10.1111/his.12264.

●● Enlace al texto completo (gratis o de pago) [1111/his.12264](#)

**AUTORES / AUTHORS:** - Jakobsen JN; Santoni-Rugiu E; Sorensen JB

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Rigshospitalet, Copenhagen, Denmark.

**RESUMEN / SUMMARY:** - AIMS: It is of interest whether expression of potentially predictive biomarkers changes during chemotherapy, for accurate evaluation after first-line chemotherapy. This study aimed to evaluate changes in RRM1 expression during chemotherapy. MATERIALS AND METHODS: RRM1 immunohistochemistry was performed on tumour samples from a total of 118 NSCLC patients with stage T1-4N0-2M0 disease. Samples were included from 65 patients treated with paclitaxel and carboplatin before surgery [neoadjuvant chemotherapy (NAC) group], and 53 patients who had undergone surgery but not chemotherapy [operation (OP) group]. RESULTS: Discordant RRM1 expression (low versus high) was observed in 32% and 43% of paired diagnostic and subsequent resection specimens in the OP group and NAC group, respectively ( $P = 0.913$ ). Ten (33%) and 12 (23%) tumours in the NAC group and the OP group, respectively, had increased RRM1 expression in the resection specimens ( $P = 0.289$ ), and 12 (40%) and 19 (36%) tumours had decreased expression ( $P = 0.707$ ). Eleven (50%) lymph node metastases had higher RRM1 expression following chemotherapy, and two (7%) had decreased expression. CONCLUSIONS: The substantial discordance between paired samples emphasizes the need for sufficient tumour tissue in biopsies when RRM1 expression is evaluated. No change in RRM1 expression was observed in primary tumours, but expression seemed to be higher in N2 lymph node metastases following chemotherapy. Tumour

heterogeneity and potential post-chemotherapy changes should be considered when RRM1 expression is evaluated.

[226]

**TÍTULO / TITLE:** - Gene expression profiling-derived immunohistochemistry signature with high prognostic value in colorectal carcinoma.

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

**REVISTA / JOURNAL:** - Gut. 2013 Oct 30. doi: 10.1136/gutjnl-2013-305475.

●● [Enlace al texto completo \(gratis o de pago\) 1136/gutjnl-2013-305475](#)

**AUTORES / AUTHORS:** - Chang W; Gao X; Han Y; Du Y; Liu Q; Wang L; Tan X; Zhang Q; Liu Y; Zhu Y; Yu Y; Fan X; Zhang H; Zhou W; Wang J; Fu C; Cao G

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology, Second Military Medical University, , Shanghai, China.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Gene expression profiling provides an opportunity to develop robust prognostic markers of colorectal carcinoma (CRC). However, the markers have not been applied for clinical decision making. We aimed to develop an immunohistochemistry signature using microarray data for predicting CRC prognosis. **DESIGN:** We evaluated 25 CRC gene signatures in independent microarray datasets with prognosis information and constructed a subnetwork using signatures with high concordance and repeatable prognostic values. Tumours were examined immunohistochemically for the expression of network-centric and the top overlapping molecules. Prognostic values were assessed in 682 patients from Shanghai, China (training cohort) and validated in 343 patients from Guangzhou, China (validation cohort). Median follow-up duration was 58 months. All p values are two-sided. **RESULTS:** Five signatures were selected to construct a subnetwork. The expression of GRB2, PTPN11, ITGB1 and POSTN in cancer cells, each significantly associated with disease-free survival, were selected to construct an immunohistochemistry signature. Patients were dichotomised into high-risk and low-risk subgroups with an optimal risk score (1.55). Compared with low-risk patients, high-risk patients had shorter disease-specific survival (DSS) in the training (HR=6.62; 95% CI 3.70 to 11.85) and validation cohorts (HR=3.53; 95% CI 2.13 to 5.84) in multivariate Cox analyses. The signature better predicted DSS than did tumour-node-metastasis staging in both cohorts. In those who received postoperative chemotherapy, high-risk score predicted shorter DSS in the training (HR=6.35; 95% CI 3.55 to 11.36) and validation cohorts (HR=5.56; 95% CI 2.25 to 13.71). **CONCLUSIONS:** Our immunohistochemistry signature may be clinically practical for personalised prediction of CRC prognosis.

[227]

**TÍTULO / TITLE:** - No association found between CYP2D6 genotype and early breast cancer events in tamoxifen-treated patients.

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

**REVISTA / JOURNAL:** - Acta Oncol. 2013 Oct 14.

●● [Enlace al texto completo \(gratis o de pago\) 3109/0284186X.2013.840739](#)

**AUTORES / AUTHORS:** - Markkula A; Hjertberg M; Rose C; Ingvar C; Jernstrom H

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

**RESUMEN / SUMMARY:** - Background. CYP2D6 is considered the key enzyme in tamoxifen metabolism. Several studies have investigated the relationship between the CYP2D6 genotype and tamoxifen treatment outcome, with discrepant results. CYP2D6 inhibitor use, aromatase inhibitor use, and chemotherapy may account for some of the discrepancies. We examined the association between CYP2D6 genotype and early breast cancer events in tamoxifen-treated breast cancer patients, in relation to CYP2D6 inhibitor use, aromatase inhibitor use, and chemotherapy. Material and methods. Pre- and postoperative questionnaires on lifestyle and concomitant medications were completed by 634 primary breast cancer patients between 2002 and 2008, among whom 333 patients had ER-positive tumors and received tamoxifen. CYP2D6\*3, \*4, \*6, \*10 and \*41 were genotyped. Information on clinical data, breast cancer events, and tumor characteristics was obtained from patients' charts, population registries, the Regional Tumor Registry, and pathology reports. Results. Median follow-up was 4.9 years. Neither poor metabolizers (adjusted HR 0.50; 95% CI 0.07-3.82) nor intermediate metabolizers (adjusted HR 1.00; 95% CI 0.47-2.11) had an increased risk of early breast cancer events when compared with extensive metabolizers. CYP2D6 activity score (taking into account genotype and CYP2D6 inhibitor use) was not associated with early breast cancer events (LogRank, P<sub>trend</sub> = 0.44). Conclusions. CYP2D6 genotype was not associated with tamoxifen treatment outcome, even when CYP2D6 inhibitor use, aromatase inhibitor use, or chemotherapy was taken into account. CYP2D6 genotype may be of minor importance for tamoxifen-treated patients in Scandinavia.

[228]

**TÍTULO / TITLE:** - Midazolam as a phenotyping probe to predict sunitinib exposure in patients with cancer.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Oct 23.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2322-7](#)

**AUTORES / AUTHORS:** - de Wit D; Gelderblom H; Sparreboom A; den Hartigh J; den Hollander M; Konig-Quartel JM; Hessing T; Guchelaar HJ; van Erp NP

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.

**RESUMEN / SUMMARY:** - PURPOSE: Patients treated with sunitinib show substantial inter-patient variability in drug exposure (~30-40 %), which is largely unexplained. Since sunitinib is metabolized by cytochrome P450(CYP)3A4, variability in the activity of this enzyme may explain a considerable proportion of this inter-patient variability. Midazolam is widely used as a phenotyping probe to assess CYP3A4-activity. The objective of this study was to prospectively evaluate the relationship between midazolam and sunitinib exposure. Additionally, the correlation between sunitinib trough levels and exposure and the influence of sunitinib on midazolam exposure was determined. METHODS: Thirteen patients treated with sunitinib in a 4 weeks "on"-2 weeks "off" regimen received twice 7.5 mg midazolam; once with and once without sunitinib. Steady-state sunitinib, its active metabolite SU12662 and midazolam exposures were determined. RESULTS: A significant correlation between midazolam exposure (AUC<sub>0-7h</sub>) and steady-state sunitinib and sunitinib + SU12662 exposure (AUC<sub>0-24h</sub>) was found (p = 0.006 and p = 0.0018, respectively); midazolam exposure

explained 51 and 41 % of the inter-patient variability in sunitinib and sunitinib + SU12622 exposure. Furthermore, C trough was highly correlated ( $r^2 = 0.94$ ) with sunitinib AUC<sub>0-24h</sub>. Sunitinib decreased midazolam exposure with 24 % ( $p = 0.034$ ). CONCLUSION: Midazolam exposure is highly correlated with sunitinib exposure and explains a large proportion of the observed inter-patient variability in sunitinib pharmacokinetics. Consequently, midazolam could be used to identify patients that are at risk of under- or overtreatment, respectively, at the start of sunitinib therapy. Moreover, sunitinib and sunitinib + SU12662 trough levels are highly correlated with drug exposure and can thus be used in clinical practice to individualize sunitinib therapy. The decrease in midazolam exposure by sunitinib needs further investigation.

[229]

**TÍTULO / TITLE:** - A phase I, open-label, single-arm, dose-escalation study of E7107, a precursor messenger ribonucleic acid (pre-mRNA) splicing inhibitor administered intravenously on days 1 and 8 every 21 days to patients with solid tumors.

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

**REVISTA / JOURNAL:** - Invest New Drugs. 2013 Nov 22.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10637-013-0046-5](#)

**AUTORES / AUTHORS:** - Hong DS; Kurzrock R; Naing A; Wheler JJ; Falchook GS; Schiffman JS; Faulkner N; Pilat MJ; O'Brien J; Lorusso P

**INSTITUCIÓN / INSTITUTION:** - University of Texas M.D. Anderson Cancer Center, Unit 455, PO Box 301402, Houston, TX, 77030, USA, [dshong@mdanderson.org](mailto:dshong@mdanderson.org).

**RESUMEN / SUMMARY:** - The aim of this study was to determine the maximum tolerated dose, dose-limiting toxicities, and pharmacokinetic profile of E7107 in patients with advanced solid tumors. Patients in this phase I, open-label, single-arm, dose-escalation study had metastatic or locally advanced solid tumors and received E7107 as a 30-minute intravenous infusion at doses of 0.6, 1.2, 1.8, 2.4, 3.2, 4.3, and 5.7 mg/m<sup>2</sup>. Twenty-six patients were enrolled in the study. At 5.7 mg/m<sup>2</sup>, two patients experienced dose-limiting toxicities including diarrhea, vomiting, dehydration, and myocardial infarction on Days 1-3 following E7107 administration. Three additional patients were recruited at the lower dose and all six patients tolerated E7107 4.3 mg/m<sup>2</sup> with no dose-limiting toxicities. The maximum tolerated dose of E7107 was therefore 4.3 mg/m<sup>2</sup>. The most common drug-related adverse events were nausea, vomiting, and diarrhea. Vision loss was experienced by two patients at Cycles 2 and 7, each patient receiving 3.2 mg/m<sup>2</sup> and 4.3 mg/m<sup>2</sup>, respectively. This resulted in the study being put on clinical hold. Pharmacokinetic analysis showed that E7107 was rapidly distributed with a moderate elimination half-life (6-13 h) and high clearance. Exposure to E7107 was dose-related. The best tumor response was stable disease in eight patients. E7107 is a unique first-in-class molecule. The incidence of two cases of vision loss probably related to E7107 led to study discontinuation.

[230]

**TÍTULO / TITLE:** - Role of endoplasmic reticulum stress induction by the plant toxin, persin, in overcoming resistance to the apoptotic effects of tamoxifen in human breast cancer cells.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 31. doi: 10.1038/bjc.2013.693.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.693](http://dx.doi.org/10.1038/bjc.2013.693)

**AUTORES / AUTHORS:** - McCloy RA; Shelley EJ; Roberts CG; Boslem E; Biden TJ; Nicholson RI; Gee JM; Sutherland RL; Musgrove EA; Burgess A; Butt AJ

**INSTITUCIÓN / INSTITUTION:** - The Kinghorn Cancer Centre, Cancer Research Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia.

**RESUMEN / SUMMARY:** - Background: Persin is a plant toxin that displays synergistic cytotoxicity with tamoxifen in human breast cancer cell lines. Here, we examined the ability of persin to circumvent tamoxifen resistance and delineated the intracellular signalling pathways involved. Methods: The induction of apoptosis in tamoxifen-resistant and -sensitive breast cancer cells was measured by flow cytometry following treatment with persin +/- tamoxifen. Markers of endoplasmic reticulum stress (ERS) were analysed following treatment, and their causal role in mediating persin-induced apoptosis was determined using chemical inhibitors and RNA interference. Results: Cells that were resistant to an apoptotic concentration of tamoxifen maintained an apoptotic response to persin. Persin-induced apoptosis was associated with an increase in markers of ERS, that is, CHOP expression and XBP-1 splicing and was decreased by CHOP siRNA. The CASP-4 inhibitor Z-YVAD-FMK markedly inhibited persin-induced apoptosis in both tamoxifen-sensitive and -resistant cells. Conclusion: The cytotoxic effects of persin are CASP-4 dependent and mediated by CHOP-dependent and -independent ERS signalling cascades. Increased ERS signalling contributes to persin-induced reversal of tamoxifen resistance. British Journal of Cancer advance online publication, 31 October 2013; doi:10.1038/bjc.2013.693 [www.bjancer.com](http://www.bjancer.com).

[231]

**TÍTULO / TITLE:** - Predicting Skin Toxicity According to EGFR Polymorphisms in Patients with Colorectal Cancer Receiving Antibody Against EGFR.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):4995-8.

**AUTORES / AUTHORS:** - Saito R; Suzuki H; Yamada T; Endo S; Moriwaki T; Ueno T; Hirose M; Hirai S; Yamato K; Mizokami Y; Hyodo I

**INSTITUCIÓN / INSTITUTION:** - 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. [hideoszk@md.tsukuba.ac.jp](mailto:hideoszk@md.tsukuba.ac.jp).

**RESUMEN / SUMMARY:** - Background/Aim: Monoclonal antibodies against epidermal growth factor receptor (EGFR) can extend progression-free survival (PFS) and overall survival (OS) in patients with unresectable colorectal cancer; however, skin toxicity often interferes with therapy continuation. PATIENTS AND METHODS: We analyzed the polymorphisms in EGFR and IgG fragment C receptor (FCGR) genes and determined their associations with clinical outcomes including PFS, OS, and skin toxicity. Five polymorphisms in EGFR and FCGR genes in 32 patients with unresectable colorectal cancer who were treated with antibodies against EGFR were examined. RESULTS: Patients carrying the C/C genotype of the EGFR D994D polymorphism displayed significantly less skin toxicity than those with other genotypes, although no significant differences in PFS and OS were noted and no significant interactions were detected for other gene polymorphisms. CONCLUSION: These

results suggest that the EGFR D994D polymorphism is a useful biomarker for predicting the severity of skin toxicity in patients receiving antibody against EGFR.

[232]

**TÍTULO / TITLE:** - Tumor necrosis therapy antibody interleukin-2 fusion protein elicits prolonged and targeted antitumor effects in vivo.

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

**REVISTA / JOURNAL:** - Appl Microbiol Biotechnol. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1007/s00253-013-5349-0](#)

**AUTORES / AUTHORS:** - Ye L; Fan J; Shi X; Tao Q; Ye D; Xian Z; Zeng X; Li Y; Feng M; Ju D

**INSTITUCIÓN / INSTITUTION:** - Department of Biosynthesis & Key Lab of Smart Drug Delivery MOE, School of Pharmacy, Fudan University, 826 Zhang Heng Road, Shanghai, 201203, China.

**RESUMEN / SUMMARY:** - Interleukin-2 (IL-2) is one of the most successful cytokines applied in tumor immunotherapy because of its ability to stimulate potent cellular immune response. The life-threatening toxicity of vascular leak syndrome (VLS) associated with the high-dose IL-2 treatment regimen has limited its use in tumor immunotherapy. To reverse this situation, a tumor-targeted fusion protein, recombinant human TNT-IL2 (rhTNT-IL2), was generated with both the cytokine activity of IL-2 and the tumor-targeting ability of TNT antibody. TNT is a human tumor necrosis therapy monoclonal antibody capable of binding intracellular antigens which are accessible and abundant in necrotic regions of tumors. The immunotherapeutic potential of this fusion protein was tested in murine melanoma and lung cancer models, and tumor-bearing mice showed satisfied tumor regressions after rhTNT-IL2 immunotherapy. Immunohistochemical study showed a distinct penetration of IL-2 in tumors in mice treated with rhTNT-IL2, indicating its evident tumor-targeting activity. Moreover, the rhTNT-IL2 was well tolerated in cynomolgus monkeys in a 12-week long-term repeated toxicity study. These studies indicate that the targeting of IL-2 to necrotic areas of tumors might be a new approach for the immunotherapy of solid tumors.

[233]

**TÍTULO / TITLE:** - Aromatase inhibitor therapy and hair loss among breast cancer survivors.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov;142(2):435-43. doi: 10.1007/s10549-013-2744-2. Epub 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2744-2](#)

**AUTORES / AUTHORS:** - Gallicchio L; Calhoun C; Helzlsouer KJ

**INSTITUCIÓN / INSTITUTION:** - The Prevention and Research Center, The Weinberg Center for Women's Health and Medicine, Mercy Medical Center, 227 St. Paul Place, Baltimore, MD, 21202, USA, [lgallic@mdmercy.com](mailto:lgallic@mdmercy.com).

**RESUMEN / SUMMARY:** - The objective of this study was to examine the associations between aromatase inhibitor therapy and hair loss or hair thinning among female breast cancer survivors. Data were analyzed from 851 female breast cancer survivors who responded to a hospital registry-based survey. Data on hair loss, hair thinning,

demographic characteristics, and health habits were based on self-report; data on aromatase inhibitor therapy were collected on the survey and verified using medical record review. Logistic regression was used to estimate the odds ratios (ORs) and 95 % confidence intervals (CIs) for the associations between aromatase inhibitor therapy and the hair outcome variables adjusted for potential confounders, including age and chemotherapy treatment. The results showed that 22.4 % of the breast cancer survivors reported hair loss and 31.8 % reported hair thinning. In the confounder-adjusted analyses, breast cancer survivors who were within 2 years of starting aromatase inhibitor treatment at the time of survey completion were approximately two and a half times more likely to report reporting hair loss (OR 2.55; 95 % CI 1.19-5.45) or hair thinning (OR 2.33; 95 % CI 1.10-4.93) within the past 4 weeks compared to those who were never treated with an aromatase inhibitor. Current aromatase inhibitor use for two or more years at the time of the survey and prior use were significantly associated with hair thinning (current users,  $\geq 2$  years: OR 1.86; prior users: OR 1.62), but not hair loss. Findings from this study suggest that aromatase inhibitor use is associated with an increased risk of hair loss and hair thinning independent of chemotherapy and age; these side effects are likely due to the substantial decrease in estrogen concentrations resulting from treatment with this drug. Future research should focus on examining these associations in a prospective manner using more detailed and objective measures of hair loss and thinning.

[234]

**TÍTULO / TITLE:** - (13)C-uracil breath test to predict 5-fluorouracil toxicity in gastrointestinal cancer patients.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Dec;72(6):1273-82. doi: 10.1007/s00280-013-2309-4. Epub 2013 Oct 8.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2309-4](#)

**AUTORES / AUTHORS:** - Cunha-Junior GF; De Marco L; Bastos-Rodrigues L; Bolina MB; Martins FL; Pianetti GA; Cesar IC; Coelho LG

**INSTITUCIÓN / INSTITUTION:** - Instituto Alfa de Gastroenterologia, Hospital das Clinicas da Universidade Federal de Minas Gerais, Av. Professor Alfredo Balena, 110, Belo Horizonte, MG, 30130-100, Brazil, [geraldo.onco@gmail.com](mailto:geraldo.onco@gmail.com).

**RESUMEN / SUMMARY:** - PURPOSE: Up to 30 % of patients undergoing 5-fluorouracil (5FU)-based chemotherapy experience severe toxicity. Dihydropyrimidine dehydrogenase (DPD) deficiency explains 36-61 % of cases. Predicting toxicity is an unmet challenge. Uracil breath test (UraBT) consists of measuring (13)CO<sub>2</sub> in exhaled breath after ingestion of 2-(13)C-uracil to evaluate pyrimidine (and 5FU) catabolism. METHODS: We studied 33 gastrointestinal cancer patients previously exposed to 5FU: Thirteen had grade 3-4 and 20, grade 0-1 toxicity. The following tests were used to evaluate pyrimidine catabolism: (1) sequencing of three exons of DPYD; (2) plasma dihydrouracil/uracil ratio (UH<sub>2</sub>/U); and (3) UraBT. We tested the performance of UraBT to discriminate patients who had grade 0-1 toxicity versus grade 3-4 toxicity and patients with and without proven DPD deficiency. RESULTS: Of the thirteen patients, four grade 3-4 toxicity patients were proved to be DPD-deficient: Three had deleterious mutations (IVS14 + 1G>A in one; single nucleotide polymorphism 2846A>T in two), and one had low UH<sub>2</sub>/U ratio. Mean delta over baseline in 50 min (DOB50)

significantly differed between groups. DOB50 $\leq$ 161.4 discriminated individuals with grade 3-4 versus grade 0-1 toxicity (sensitivity = 61.5 %; specificity = 85 %) and DPD-deficient versus non-DPD-deficient (sensitivity = 75 %; specificity = 85 %).  
CONCLUSION: UraBT has moderate accuracy in discriminating individuals who manifested severe toxicity from those who had mild or no toxicity to 5FU.

[235]

**TÍTULO / TITLE:** - Chaetoglobosin A preferentially induces apoptosis in chronic lymphocytic leukemia cells by targeting the cytoskeleton.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Nov 27. doi: 10.1038/leu.2013.360.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.360](#)

**AUTORES / AUTHORS:** - Knudsen PB; Hanna B; Ohl S; Sellner L; Zenz T; Dohner H; Stilgenbauer S; Larsen TO; Lichter P; Seiffert M

**INSTITUCIÓN / INSTITUTION:** - 1] German Cancer Research Center (DKFZ), Division of Molecular Genetics, Heidelberg, Germany [2] Technical University of Denmark (DTU), Department of Systems Biology, Lyngby, Denmark.

**RESUMEN / SUMMARY:** - Chronic lymphocytic leukemia (CLL) is an incurable malignancy of mature B cells. One of the major challenges in treatment of CLL is the achievement of a complete remission to prevent relapse of disease originating from cells within lymphoid tissues and subsequent chemoresistance. In search for novel drugs that target CLL cells also in protective microenvironments, we performed a fungal extract screen using cocultures of primary CLL cells with bone marrow-derived stromal cells. A metabolite produced by *Penicillium aquamarinum* was identified as Chaetoglobosin A, a member of the cytochalasan family that showed preferential induction of apoptosis in CLL cells, even under culture conditions that mimic lymphoid tissues. In vitro testing of 89 CLL cases revealed effective targeting of CLL cells by Chaetoglobosin A, independent of bad prognosis characteristics, like 17p deletion or TP53 mutation. To provide insight into its mechanism of action, we showed that ChA targets filamentous actin in CLL cells and thereby induces cell cycle arrest and inhibits membrane ruffling and cell migration. Our data further revealed that Chaetoglobosin A prevents CLL cell activation and sensitizes them for treatment with PI3K and BTK inhibitors, suggesting this compound as a novel potential drug for CLL. Leukemia accepted article preview online, 27 November 2013. doi:10.1038/leu.2013.360.

[236]

**TÍTULO / TITLE:** - Sequence-dependent combination therapy with doxorubicin and a survivin-specific small interfering RNA nanodrug demonstrates efficacy in models of adenocarcinoma.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 1. doi: 10.1002/ijc.28499.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28499](#)

**AUTORES / AUTHORS:** - Ghosh SK; Yigit MV; Uchida M; Ross AW; Barteneva N; Moore A; Medarova Z

**INSTITUCIÓN / INSTITUTION:** - Molecular Imaging Laboratory, MGH/HST Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA.

**RESUMEN / SUMMARY:** - The clinical management of cancer reflects a balance between treatment efficacy and toxicity. While typically, combination therapy improves response rate and time to progression compared with sequential monotherapy, it causes increased toxicity. Consequently, in cases of advanced cancer, emerging guidelines recommend sequential monotherapy, as a means to enhance quality of life. An alternative approach that could overcome nonspecific toxicity while retaining therapeutic efficacy, involves the combination of chemotherapy with targeted therapy. In the current study, we tested the hypothesis that combination therapy targeting survivin (BIRC5) and low-dose doxorubicin (Dox) will show enhanced therapeutic potential in the treatment of cancer, as compared to monotherapy with Dox. We demonstrate in both in vitro and in vivo models of breast cancer that combination therapy with a low dose of Dox and an anti-survivin siRNA nanodrug (MN-siBIRC5) is superior to mono-therapy with either low- or high-dose Dox alone. Importantly, therapeutic efficacy showed prominent sequence dependence. Induction of apoptosis was observed only when the cells were treated with Dox followed by MN-siBIRC5, whereas the reverse sequence abrogated the benefit of the drug combination. In vivo, confirmation of successful sequence dependent combination therapy was demonstrated in a murine xenograft model of breast cancer. Finally, to determine if the observed effect is not limited to breast cancer, we extended our studies to a murine xenograft model of pancreatic adenocarcinoma and found similar outcomes as shown for breast cancer.

[237]

**TÍTULO / TITLE:** - Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: An analysis of the surveillance, epidemiology and end results database.

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

**REVISTA / JOURNAL:** - Am J Hematol. 2013 Nov 23. doi: 10.1002/ajh.23638.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ajh.23638](#)

**AUTORES / AUTHORS:** - Castillo JJ; Winer ES; Olszewski AJ

**INSTITUCIÓN / INSTITUTION:** - Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA, USA.

**RESUMEN / SUMMARY:** - Introduction: Approximately a third of the patients with diffuse large B-cell lymphoma present with extranodal involvement. Our study aims to identify primary extranodal sites of disease associated with prognosis in patients with DLBCL in the rituximab era. A secondary objective is to describe epidemiological and clinical characteristics of patients with extranodal DLBCL. Methods: We included adult patients from the SEER database (2004-2009) in whom DLBCL was the first malignancy diagnosed. Extranodal primary sites were divided into 12 groups according to the topography code reported by SEER. Multivariate overall survival (OS) analyses were performed using Cox proportional-hazard regression models adjusted for age, sex, race and stage. Results: From a total of 25,992 adult DLBCL patients included in our analysis, 32% presented with extranodal primary sites. Gastrointestinal tract (34%), head/neck (H&N; 14%) and skin/soft tissue (11%) were the most common. In

comparison with nodal DLBCL, patients with extranodal involvement were older (with exception of skeletal sites) and presented with earlier stages. In the multivariate analysis, sites associated with worse OS rates were gastrointestinal (HR 1.24, 95% CI 1.15-1.33;  $p < 0.001$ ), pulmonary (HR 1.59, 95% CI 1.38-1.83;  $p < 0.001$ ) and liver/pancreas (HR 1.58, 95% CI 1.35-1.85;  $p < 0.001$ ) while H&N was associated with better survival (HR 0.79, 95% CI 0.70-0.89;  $p < 0.001$ ). Conclusion: In this population-based study, primary extranodal sites of involvement are associated with distinct outcomes in patients with DLBCL. Gastrointestinal, pulmonary and liver/pancreas sites had a significant worse outcome than nodal sites.

[238]

**TÍTULO / TITLE:** - The prognostic value of Smad4 mRNA in patients with prostate cancer.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 24.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1439-y](#)

**AUTORES / AUTHORS:** - Zhang DT; Shi JG; Liu Y; Jiang HM

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, First Affiliated Hospital of Liaoning Medical University, Jinzhou, 121001, China.

**RESUMEN / SUMMARY:** - The tumor suppressor gene Smad4 has been localized to chromosome 18q21.1 and is a member of the Smad family that mediates the transforming growth factor beta signaling pathway suppressing epithelial cell growth. However, variable expression of Smad4 messenger RNA (mRNA) has been reported, with a loss in some cancers and increased expression in others. The aim of the present study was to investigate the Smad4 mRNA expression in prostate cancer tissues and adjacent noncancerous tissues and its potential relevance to clinicopathological variables and prognosis. The expression change of Smad4 mRNA was detected by using real-time quantitative reverse transcriptase-polymerase chain reaction analysis. The data showed that the Smad4 mRNA expression level in prostate cancer tissues was significantly lower than those in noncancerous tissues. The results indicated that the low expression of Smad4 mRNA in prostate cancer was associated with lymph node metastasis, preoperative prostate-specific antigen (PSA), and Gleason score. Kaplan-Meier survival analysis showed that patients with high Smad4 mRNA expression have longer biochemical recurrence-free survival time compared to patients with low Smad4 mRNA expression. Multivariate analysis revealed that Smad4 mRNA expression was an independent predictor of biochemical recurrence-free survival. Our results emphasize that Smad4 mRNA can be used as a predictive biomarker.

[239]

**TÍTULO / TITLE:** - Elevated phenylacetic acid levels do not correlate with adverse events in patients with urea cycle disorders or hepatic encephalopathy and can be predicted based on the plasma PAA to PAGN ratio.

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

**REVISTA / JOURNAL:** - Mol Genet Metab. 2013 Dec;110(4):446-53. doi: 10.1016/j.ymgme.2013.09.017. Epub 2013 Oct 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.ymgme.2013.09.017](#)

**AUTORES / AUTHORS:** - Mokhtarani M; Diaz GA; Rhead W; Berry SA; Lichter-Konecki U; Feigenbaum A; Schulze A; Longo N; Bartley J; Berquist W; Gallagher R; Smith W; McCandless SE; Harding C; Rockey DC; Vierling JM; Mantry P; Ghabril M; Brown RS Jr; Dickinson K; Moors T; Norris C; Coakley D; Milikien DA; Nagamani SC; Lemons C; Lee B; Scharschmidt BF

**INSTITUCIÓN / INSTITUTION:** - Hyperion Therapeutics, 601 Gateway Blvd., Suite 200, South San Francisco, CA 94080, USA. Electronic address:

[Masoud.mokhtarani@hyperiontx.com](mailto:Masoud.mokhtarani@hyperiontx.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Phenylacetic acid (PAA) is the active moiety in sodium phenylbutyrate (NaPBA) and glycerol phenylbutyrate (GPB, HPN-100). Both are approved for treatment of urea cycle disorders (UCDs) - rare genetic disorders characterized by hyperammonemia. PAA is conjugated with glutamine in the liver to form phenylacetylgutamine (PAGN), which is excreted in urine. PAA plasma levels  $\geq 500$   $\mu\text{g}/\text{dL}$  have been reported to be associated with reversible neurological adverse events (AEs) in cancer patients receiving PAA intravenously. Therefore, we have investigated the relationship between PAA levels and neurological AEs in patients treated with these PAA pro-drugs as well as approaches to identifying patients most likely to experience high PAA levels. METHODS: The relationship between nervous system AEs, PAA levels and the ratio of plasma PAA to PAGN were examined in 4683 blood samples taken serially from: [1] healthy adults [2], UCD patients of  $\geq 2$  months of age, and [3] patients with cirrhosis and hepatic encephalopathy (HE). The plasma ratio of PAA to PAGN was analyzed with respect to its utility in identifying patients at risk of high PAA values. RESULTS: Only 0.2% (11) of 4683 samples exceeded 500  $\mu\text{g}/\text{mL}$ . There was no relationship between neurological AEs and PAA levels in UCD or HE patients, but transient AEs including headache and nausea that correlated with PAA levels were observed in healthy adults. Irrespective of population, a curvilinear relationship was observed between PAA levels and the plasma PAA:PAGN ratio, and a ratio  $> 2.5$  (both in  $\mu\text{g}/\text{mL}$ ) in a random blood draw identified patients at risk for PAA levels  $> 500$   $\mu\text{g}/\text{mL}$ . CONCLUSIONS: The presence of a relationship between PAA levels and reversible AEs in healthy adults but not in UCD or HE patients may reflect intrinsic differences among the populations and/or metabolic adaptation with continued dosing. The plasma PAA:PAGN ratio is a functional measure of the rate of PAA metabolism and represents a useful dosing biomarker.

[240]

**TÍTULO / TITLE:** - Magnetic resonance imaging/positron emission tomography provides a roadmap for surgical planning and serves as a predictive biomarker in patients with recurrent gynecological cancers undergoing pelvic exenteration.

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

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 Oct;23(8):1512-9. doi: 10.1097/IGC.0b013e3182a41e61.

●● Enlace al texto completo (gratis o de pago) [1097/IGC.0b013e3182a41e61](#)

**AUTORES / AUTHORS:** - Vargas HA; Burger IA; Donati OF; Andikyan V; Lakhman Y; Goldman DA; Schoder H; Chi DS; Sala E; Hricak H

**INSTITUCIÓN / INSTITUTION:** - Departments of \*Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY; †Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland; and double

Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.

**RESUMEN / SUMMARY:** - OBJECTIVE: Magnetic resonance imaging (MRI) is the modality of choice for staging gynecological cancers owing to its superb soft tissue resolution, whereas F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) allows the assessment of glycolytic activity within the tumor microenvironment. In this study, we evaluated the incremental value of fused MRI/PET over MRI or fluorodeoxyglucose PET/CT alone for assessing local disease extent in patients with recurrent gynecological cancers undergoing pelvic exenteration and determined the associations between imaging findings and clinical outcomes in this patient population. MATERIALS AND METHODS: The institutional review board approved this retrospective, Health Insurance Portability and Accountability Act (HIPAA)-compliant study of 31 patients who underwent pelvic MRI and PET/CT 3 months or less before pelvic exenteration for recurrent cancers of the uterine cervix, corpus, or vulva/vagina. Using a 1 to 5 scale (1, definitely not present; 5, definitely present), 2 readers independently evaluated MRI, PET/CT, and fused MRI/PET images for the presence of bladder, rectum, and pelvic sidewall invasion. Surgical pathology constituted the reference standard. Measurements of diagnostic accuracy, interreader agreement, and associations between imaging findings and progression-free survival and overall survival were calculated. RESULTS: Compared with MRI or PET/CT, fused MRI/PET correctly improved readers' diagnostic confidence in detecting bladder, rectum, or pelvic sidewall invasion in up to 52% of patients. Interreader agreement was consistently in the highest ("almost perfect") range only for MRI/PET (kappa = 0.84-1.0). The highest sensitivities (0.82-1.0), specificities (0.91-1.0), and predictive values (0.80-1.0) were consistently achieved with fused MRI/PET (although the differences were not statistically significant [P > 0.05]). Pelvic sidewall invasion on MRI/PET was the only finding significantly associated with both progression-free and overall survival for both readers (P = 0.0067-0.0440). CONCLUSIONS: In patients with recurrent gynecological cancers undergoing pelvic exenteration, fused MRI/PET served as a predictive biomarker and yielded greater diagnostic confidence and interreader agreement than either MRI or PET/CT.

[241]

**TÍTULO / TITLE:** - Hyaluronic acid-drug conjugate of docetaxel and metformin to target cancer cells and cancer stem cells: Synthesis and characterization.

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

**REVISTA / JOURNAL:** - J Control Release. 2013 Nov 28;172(1):e59. doi: 10.1016/j.jconrel.2013.08.122.

●● Enlace al texto completo (gratis o de pago) [1016/j.jconrel.2013.08.122](#)

**AUTORES / AUTHORS:** - Goodarzi N; Amini M; Ghahremani MH; Atyabi F; Ostad SN; Dinarvand R

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 1417614411, Iran. Electronic address: [Goodarzi\\_n@tums.ac.ir](mailto:Goodarzi_n@tums.ac.ir).

[242]

**TÍTULO / TITLE:** - Smac mimetic compound LCL161 sensitizes esophageal carcinoma cells to radiotherapy by inhibiting the expression of inhibitor of apoptosis protein.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 30.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1338-2](#)

**AUTORES / AUTHORS:** - Qin Q; Zuo Y; Yang X; Lu J; Zhan L; Xu L; Zhang C; Zhu H; Liu J; Liu Z; Tao G; Dai S; Zhang X; Ma J; Cai J; Sun X

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, China.

**RESUMEN / SUMMARY:** - Currently, unresectable esophageal squamous cell carcinoma (ESCC) is primarily treated by chemoradiotherapy. However, the outcome has not improved significantly due to radioresistance of cancer cells. This study aimed to determine the radiosensitizing effect of LCL161, a novel second mitochondrial-derived activator of caspase (Smac) mimetic, in ESCC cells. ESCC cell lines were treated with LCL161 or radiation, alone or in combination. Cell proliferation was detected by MTT assay. Radiosensitization was evaluated by clonogenic survival assay. Cell apoptosis was detected by flow cytometry. The results showed that LCL161 potently sensitized ESCC cells to radiation with a sensitization enhancement ratio of 1.4-2.0. LCL161 increased radiation-induced DNA double-stranded breaks and promoted the apoptosis of ESCC cells, which could be abrogated by a pan-caspase inhibitor z-VAD-FMK. Furthermore, LCL161 decreased the level of cIAP1 in ESCC cells in a dose-dependent manner and synthesized with irradiation to promote the activation of caspase 8 and the upregulation of TNF $\alpha$  expression in ESCC cells. In conclusion, LCL161 acts as a strong radiosensitizer in human esophageal cancer cells by inhibiting the expression of cIAP1 and promoting the activation of caspase 8, leading to enhanced apoptosis.

[243]

**TÍTULO / TITLE:** - Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1-PDGFRB fusion.

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

**REVISTA / JOURNAL:** - Haematologica. 2013 Nov;98(11):e146-8. doi: 10.3324/haematol.2013.095372.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.095372](#)

**AUTORES / AUTHORS:** - Lengline E; Beldjord K; Dombret H; Soulier J; Boissel N; Clappier E

**INSTITUCIÓN / INSTITUTION:** - [emmanuelle.clappier@rdb.aphp.fr](mailto:emmanuelle.clappier@rdb.aphp.fr).

[244]

**TÍTULO / TITLE:** - Procyanidins from Evening Primrose (*Oenothera paradoxa*) Defatted Seeds Inhibit Invasiveness of Breast Cancer Cells and Modulate the Expression of Selected Genes Involved in Angiogenesis, Metastasis, and Apoptosis.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013;65(8):1219-31. doi: 10.1080/01635581.2013.830314. Epub 2013 Oct 7.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.830314](#)

**AUTORES / AUTHORS:** - Lewandowska U; Szewczyk K; Owczarek K; Hrabec Z; Podsedek A; Sosnowska D; Hrabec E

**INSTITUCIÓN / INSTITUTION:** - a Department of Medical Enzymology , Medical University of Lodz , Lodz , Poland.

**RESUMEN / SUMMARY:** - There is a growing interest in plant polyphenols (including flavanols) that exhibit pleiotropic biological activities such as antiinflammatory, antioxidant, and anticancer effects. Here, we report for the first time the inhibition of MDA-MB-231 breast cancer cell viability and invasiveness by an evening primrose flavanol preparation (EPFP). We observed a decrease in MDA-MB-231 viability of 50% vs. a control after 72 h of incubation with EPFP at a concentration of 58 µM gallic acid equivalents (GAE) and an inhibition of their invasiveness of 65% vs. a control at 75 µM GAE after 48 h of incubation. EPFP caused a 10-fold reduction in matrix metalloproteinase-9 (MMP-9) activity at 100 µM GAE. Furthermore, through modulation of mRNA expression, EPFP reduced the expression levels of the following proteins: antiapoptotic Bcl-2, angiogenic vascular endothelial growth factor (VEGF), and 2 transcription factors (c-Jun, c-Fos). Moreover, analysis by flow cytometry revealed that EPFP induced apoptosis in MDA-MB-231 cells. In conclusion, our data shows that EPFP inhibits cell viability by increasing apoptosis and decreases cell invasiveness by decreasing angiogenesis.

[245]

**TÍTULO / TITLE:** - The gene signature in CCAAT-enhancer-binding protein alpha dysfunctional acute myeloid leukemia predicts responsiveness to histone deacetylase inhibitors.

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

**REVISTA / JOURNAL:** - Haematologica. 2013 Oct 31.

●● [Enlace al texto completo \(gratis o de pago\) 3324/haematol.2013.093278](#)

**AUTORES / AUTHORS:** - Liss A; Ooi CH; Zjablovskaja P; Benoukraf T; Radomska HS; Ju C; Wu M; Balastik M; Delwel R; Brdicka T; Tan P; Tenen DG; Alberich-Jorda M

**INSTITUCIÓN / INSTITUTION:** - Singapore;

**RESUMEN / SUMMARY:** - C/EBPalpha proteins, encoded by the CCAAT-enhancer-binding protein alpha gene, play a crucial role in granulocytic development, and defects in this transcription factor have been reported in acute myeloid leukemia. Here, we defined the C/EBPalpha signature characterized by a set of genes upregulated upon C/EBPalpha activation. We analyzed expression of the C/EBPalpha signature in a cohort of 525 acute myeloid leukemia patients and identified a subset of samples characterized by low expression of this signature. We referred to this group of patients as the C/EBPalpha dysfunctional subset. Remarkably, a large percentage of samples harboring C/EBPalpha biallelic mutations clustered within this subset. We hypothesize that re-activation of the C/EBPalpha signature in the C/EBPalpha dysfunctional subset could have therapeutic potential. In search for small molecules able to reverse the low expression of the C/EBPalpha signature we applied the Connectivity Map. This analysis predicted positive connectivity between the C/EBPalpha activation signature and histone deacetylase inhibitors. We showed that these inhibitors reactivate expression of the C/EBPalpha signature and promote granulocytic differentiation of primary samples from the C/EBPalpha dysfunctional subset harboring biallelic C/EBPalpha mutations. Altogether, our data identify histone deacetylase inhibitors as

potential candidates in the treatment of certain leukemias characterized by downregulation of the C/EBPalpha signature.

[246]

**TÍTULO / TITLE:** - A novel anthracene derivative, MHY412, induces apoptosis in doxorubicin-resistant MCF-7/Adr human breast cancer cells through cell cycle arrest and downregulation of P-glycoprotein expression.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):167-76. doi: 10.3892/ijo.2013.2160. Epub 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2160](#)

**AUTORES / AUTHORS:** - De U; Chun P; Choi WS; Lee BM; Kim ND; Moon HR; Jung JH; Kim HS

**INSTITUCIÓN / INSTITUTION:** - College of Pharmacy, Pusan National University, Busan 609-735, Republic of Korea.

**RESUMEN / SUMMARY:** - New potential chemotherapeutic strategies are required to overcome multidrug resistance (MDR) in cancer. This study investigated the anticancer effect of a novel anthracene derivative MHY412 on doxorubicin-resistant human breast cancer (MCF-7/Adr) cells. We measured cell viability and the expression of apoptosis-related genes; in addition, the antitumor activity of MHY412 was confirmed using an in vivo tumor xenograft model. MHY412 significantly inhibited the proliferation of MCF-7/Adr and MCF-7 cells in a concentration-dependent manner. Notably, the halfmaximal inhibitory concentration (IC50) values of MHY412 in MCF-7/Adr (0.15 microM) and MCF-7 (0.26 microM) cells were lower than those of doxorubicin (MCF-7/Adr, 13.6 microM and MCF-7, 1.26 microM) after treatment for 48 h. MHY412 at low concentrations induced S phase arrest, but at high concentrations, the number of MCF-7/Adr cells in the sub-G1 phase significantly increased. MHY412-induced sub-G1 phase arrest was associated with inhibition of cyclin, cyclindependent kinase 2 (CDK2) and p21 expression in MCF-7/Adr cells. MHY412 markedly reduced P-glycoprotein (P-gp) expression and increased apoptotic cell death in MCF-7/Adr cells. Cleavage of poly-ADP ribose polymerase, reduced Bcl-2 expression, and increased in cytochrome c release in MCF-7/Adr cells confirmed the above results. In addition, MHY412 markedly inhibited tumor growth in a tumor xenograft model of MCF-7/Adr cells. Our data suggest that MHY412 exerts antitumor effects by selectively modulating the genes related to cell cycle arrest and apoptosis. In particular, MHY412 is a new candidate agent for the treatment of Bcl-2 overexpressed doxorubicin-resistant human breast cancer.

[247]

**TÍTULO / TITLE:** - Clinical Implementation of Germline Cancer Pharmacogenetic Variants during the Next-Generation Sequencing Era.

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

**REVISTA / JOURNAL:** - Clin Pharmacol Ther. 2013 Oct 17. doi: 10.1038/clpt.2013.214.

●● Enlace al texto completo (gratis o de pago) [1038/clpt.2013.214](#)

**AUTORES / AUTHORS:** - Gillis NK; Patel JN; Innocenti F

**INSTITUCIÓN / INSTITUTION:** - Eshelman School of Pharmacy, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC.

**RESUMEN / SUMMARY:** - Over 100 FDA-approved medications include pharmacogenetic biomarkers in the drug label, many with cancer indications referencing germline DNA variations. With the advent of next-generation sequencing (NGS) and its rapidly increasing uptake into cancer research and clinical practice, an enormous amount of data to inform documented gene-drug associations will be collected, which must be exploited to optimize patient benefit. This state-of-the-art article focuses on the implementation of germline cancer pharmacogenetics into clinical practice. Specifically, it discusses the importance of germline variation in cancer and the role of NGS in pharmacogenetic discovery and implementation. In the context of a scenario where massive NGS-based genetic information will be increasingly available to health stakeholders, this review explores the ongoing debate over the threshold of evidence necessary for implementation, provides an overview of recommendations in cancer by professional organizations and regulatory bodies, discusses limitations of current guidelines and strategies to improve third-party coverage. *Clinical Pharmacology & Therapeutics* (2013); Accepted article preview online 17 October 2013; doi:10.1038/clpt.2013.214.

[248]

**TÍTULO / TITLE:** - Combination treatment for glioblastoma cells with tumor necrosis factor-related apoptosis-inducing ligand and oncolytic adenovirus delta-24.

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

**REVISTA / JOURNAL:** - *Cancer Invest.* 2013 Nov;31(9):630-8. doi: 10.3109/07357907.2013.849724.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.849724](#)

**AUTORES / AUTHORS:** - Tsamis KI; Alexiou GA; Vartholomatos E; Kyritsis AP

**INSTITUCIÓN / INSTITUTION:** - Neurosurgical Institute, Medical School, University of Ioannina, Ioannina, Greece.

**RESUMEN / SUMMARY:** - Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) exhibits cancer-selective killing activity representing a promising anticancer therapeutic strategy. Adenovirus Delta-24 is another interested anticancer agent selectively killing cells with a defective p16/Rb/E2F pathway. However, many types of cancer, including gliomas, could develop resistance to Delta-24 or TRAIL-induced apoptosis. In this study, we investigated whether TRAIL, in combination with adenovirus Delta-24, could result in an enhanced antiglioma effect in vitro in a panel of glioblastoma cell lines (U87MG, U251MG, D54, and T98G). The treatment of glioblastoma cell lines with TRAIL and Delta-24 adenovirus in combination showed markedly enhanced effect, compared to each agent alone.

[249]

**TÍTULO / TITLE:** - Superior antimetabolic and chemosensitization activities of the combination treatment of the histone deacetylase inhibitor apicidin and proteasome inhibitors on human colorectal cancer cells.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):105-28. doi: 10.3892/ijo.2013.2146. Epub 2013 Oct 22.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2146](https://doi.org/10.3892/ijo.2013.2146)

**AUTORES / AUTHORS:** - Abaza MS; Bahman AM; Al-Attayah R

**INSTITUCIÓN / INSTITUTION:** - Molecular Biology Program, Department of Biological Sciences, Faculty of Science, Kuwait University, Safat, Kuwait.

**RESUMEN / SUMMARY:** - Despite the effectiveness of histone deacetylase inhibitors, proteasome inhibitors and cytotoxic drugs on human cancers, none of these types of treatments by themselves has been sufficient to eradicate the disease. The combination of different modalities may hold enormous potential for eliciting therapeutic results. In the current study, we examined the effects of treatment with the histone deacetylase inhibitor (HDACI) apicidin (APC) in combination with proteasome inhibitors on human colorectal cancer cells. The molecular mechanisms of the combined treatments and their potential to sensitize colorectal cancer cells to chemotherapies were also investigated. Cancer cells were exposed to the agents alone and in combination, and cell growth inhibition was determined by MTT and colony formation assays. HDAC, proteasome and NF-kappaB activities as well as reactive oxygen species (ROS) were monitored. Cell cycle perturbation and induction of apoptosis were assessed by flow cytometry. The expression of cell cycle/apoptosis- and cytoprotective/stress-related genes was determined by quantitative PCR and EIA, respectively. The potentiation of cancer cell sensitivity to chemotherapies upon APC/PI combination treatment was also studied. The combination of APC and MG132, PI-1 or epoxomicin potently inhibited cancer cell growth, disrupted the cell cycle, induced apoptosis, decreased NF-kappaB activity and increased ROS production. These events were accompanied by the altered expression of genes associated with the cell cycle, apoptosis and cytoprotection/stress regulation. The combination treatment markedly enhanced the chemosensitivity of colorectal cancer cells (50-3.7x10<sup>4</sup>-fold) in a drug-, APC/PI combination- and colorectal cancer subtype-dependent manner. The results of this study have implications for the development of combinatorial treatments that include HDACIs, PIs and conventional chemotherapeutic drugs, suggesting a potential therapeutic synergy with general applicability to various types of cancers.

[250]

**TÍTULO / TITLE:** - Hypoxia-related gene expression profile in childhood acute lymphoblastic leukemia: prognostic implications.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Oct 28.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.858812](https://doi.org/10.3109/10428194.2013.858812)

**AUTORES / AUTHORS:** - Silveira VS; Freire BM; Borges KS; Andrade AF; Cruzeiro GA; Sabino JP; Glass ML; Yunes JA; Brandalise SR; Tone LG; Scrideli CA

**RESUMEN / SUMMARY:** - Abstract Cellular hypoxic condition is a key event in several human cancers but the knowledge about its role in childhood ALL is very limited. In the present study gene expression profile of hypoxia-related genes (HIF1A, CA9, VEGF and SCL2A1) was evaluated in bone marrow samples of 113 pediatric patients. HIF1A mRNA up-regulation was significantly associated with higher 5-years event-free survival rates in B-ALL patients as well as in the overall ALL population in both univariate and multivariate analysis (P = 0.023 and P = 0.041 respectively). In gene

expression analysis, low oxygen levels promoted HIF1A activation in a time-dependent manner, in both ALL cell lines. In vitro cytotoxic assays suggested an initial trend to hypoxia-related resistance in the first 24 hours, but later time points (48 - 72 hours) evaluation clearly showed that there is no relevant difference in drug response when comparing hypoxic to normal oxygen level conditions. Modulation of mRNA expression of several hypoxia-related genes was also observed after hypoxic exposure in a cell specific manner, suggesting that HIF1A mRNA expression could play a different role in specific subtypes of leukemia. Despite the remaining questions regarding hypoxia-mediated mechanisms, these findings could be helpful to provide new insights in the role of hypoxia in childhood ALL.

[251]

**TÍTULO / TITLE:** - Regulation of the Src-PP2A Interaction in Tumor Necrosis Factor (TNF)-related Apoptosis-inducing Ligand (TRAIL)-induced Apoptosis.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 15;288(46):33263-71. doi: 10.1074/jbc.M113.508093. Epub 2013 Oct 7.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.508093](#)

**AUTORES / AUTHORS:** - Xu J; Xu Z; Zhou JY; Zhuang Z; Wang E; Boerner J; Wu GS

**INSTITUCIÓN / INSTITUTION:** - From the Karmanos Cancer Institute, Departments of Oncology and Pathology, Wayne State University School of Medicine, Detroit, Michigan 48201.

**RESUMEN / SUMMARY:** - TNF-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in transformed and tumor cells but not in normal cells, making it a promising agent for cancer therapy. However, many cancer cells are resistant to TRAIL, and the underlying mechanisms are not fully understood. Here, we show that the regulation of the PP2A and Src interaction plays a critical role in TRAIL resistance. Specifically, we show that TRAIL treatment activates the tyrosine kinase Src, which subsequently phosphorylates caspase-8 at tyrosine 380, leading to the inhibition of caspase-8 activation. We also show that upon TRAIL treatment, Src, caspase-8, and PP2A/C (a catalytic subunit of the PP2A phosphatase) are redistributed into lipid rafts, a microdomain of the plasma membrane enriched with cholesterol, where PP2A dephosphorylates Src at tyrosine 418 and in turn inhibits caspase-8 phosphorylation. Furthermore, we find that TRAIL treatment causes PP2A/C degradation. These data suggest that the balance between Src-mediated caspase-8 phosphorylation and the inactivation of Src-mediated caspase-8 phosphorylation by PP2A determines the outcome of TRAIL treatment in breast cancer cells. Therefore, this work identifies a novel mechanism by which the interaction between PP2A and Src in the context of caspase-8 activation modulates TRAIL sensitivity in cancer cells.

[252]

**TÍTULO / TITLE:** - CYP2B6\*6 is an independent determinant of inferior response to fludarabine plus cyclophosphamide in chronic lymphocytic leukaemia.

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

**REVISTA / JOURNAL:** - Blood. 2013 Oct 15.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-07-516666](#)

**AUTORES / AUTHORS:** - Johnson GG; Lin K; Cox TF; Oates M; Sibson DR; Eccles R; Lloyd B; Gardiner LJ; Carr DF; Pirmohamed M; Strefford JC; Oscier DG; Gonzalez de Castro D; Else M; Catovsky D; Pettitt AR

**INSTITUCIÓN / INSTITUTION:** - Directorate of Blood Sciences, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom;

**RESUMEN / SUMMARY:** - Fludarabine plus cyclophosphamide (FC) is the chemotherapy backbone of modern chronic lymphocytic leukaemia (CLL) treatment. CYP2B6 is a polymorphic cytochrome P450 isoform which converts cyclophosphamide to its active form. This study was conducted to investigate the possible impact of genetic variation in CYP2B6 on response to FC chemotherapy in CLL. Available DNA samples from the LRF CLL4 trial, which compared chlorambucil, fludarabine and FC, were screened by Taqman real-time PCR assays for CYP2B6 SNPs c.516G>T and c.785A>G, which define the most common variant allele (\*6). Among the 455 samples that were successfully genotyped, 265 (58.2%), 134 (29.5%) and 29 (6.4%) were classified as \*1/\*1, \*1/\*6 and \*6/\*6, respectively. Patients expressing at least one \*6 allele were significantly less likely to achieve a complete response (CR) following FC (odds ratio 0.27; p=0.004) but not chlorambucil or fludarabine. Analysis of individual response indicators confirmed that this inferior response resulted from impaired cyto-reduction rather than delayed haemopoietic recovery. Multivariate analysis controlling for age, gender, stage, IGHV mutational status, 11q deletion and TP53 deletion/mutation identified CYP2B6\*6 and TP53 mutation/deletion as the only independent determinants of CR attainment following FC. Our study provides the first demonstration that host pharmacogenetics can influence therapeutic response in CLL. This trial is registered as an International Standard Randomised Control Trial, number NCT 58585610 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

[253]

**TÍTULO / TITLE:** - EZH2 Protein Expression Associates with the Early Pathogenesis, Tumor Progression, and Prognosis of Non-Small Cell Lung Carcinoma.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Dec 1;19(23):6556-65. doi: 10.1158/1078-0432.CCR-12-3946. Epub 2013 Oct 4.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-12-3946](#)

**AUTORES / AUTHORS:** - Behrens C; Solis LM; Lin H; Yuan P; Tang X; Kadara H; Riquelme E; Galindo H; Moran CA; Kalhor N; Swisher SG; Simon GR; Stewart DJ; Lee JJ; Wistuba II

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Thoracic/Head and Neck Medical Oncology, Pathology, Biostatistics, Thoracic Surgery, and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and The University of Ottawa, Ottawa, Canada.

**RESUMEN / SUMMARY:** - PURPOSE: Enhancer of zeste homolog 2 (EZH2) promotes carcinogenesis by epigenetically silencing tumor suppressor genes. We studied EZH2 expression by immunohistochemistry in a large series of non-small cell lung carcinomas (NSCLC) in association with tumor characteristics and patient outcomes. EXPERIMENTAL DESIGN: EZH2 immunohistochemistry expression was analyzed in 265 normal and premalignant bronchial epithelia, 541 primary NSCLCs [221 squamous

cell carcinomas (SCC) and 320 adenocarcinomas] and 36 NSCLCs with paired brain metastases. An independent set of 91 adenocarcinomas was also examined. EZH2 expression was statistically correlated with clinico-pathological information, and EGFR/KRAS mutation status. RESULTS: EZH2 expression was significantly ( $P < 0.0001$ ) higher in SCCs compared with adenocarcinomas and in brain metastasis relative to matched primary tumors ( $P = 0.0013$ ). EZH2 expression was significantly ( $P < 0.0001$ ) elevated in bronchial preneoplastic lesions with increasing severity. In adenocarcinomas, higher EZH2 expression significantly correlated with younger age, cigarette smoking, and higher TNM stage ( $P = 0.02$  to  $P < 0.0001$ ). Higher EZH2 expression in adenocarcinoma was associated with worse recurrence-free survival (RFS;  $P = 0.025$ ; HR = 1.54) and overall survival (OS;  $P = 0.0002$ ; HR = 1.96). Furthermore, lung adenocarcinomas with low EZH2 levels and high expression of the lineage-specific transcription factor, TTF-1, exhibited significantly improved RFS ( $P = 0.009$ ; HR = 0.51) and OS ( $P = 0.0011$ ; HR = 0.45), which was confirmed in the independent set of 91 adenocarcinomas. CONCLUSION: In lung, EZH2 expression is involved in early pathogenesis of SCC and correlates with a more aggressive tumor behavior of adenocarcinoma. When EZH2 and TTF-1 expressions are considered together, they serve as a prognostic marker in patients with surgically resected lung adenocarcinomas. Clin Cancer Res; 19(23); 6556-65. ©2013 AACR.

[254]

**TÍTULO / TITLE:** - Case with chronic myeloid leukemia and T315I mutation, but still in complete molecular response under high dose imatinib therapy.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.850164](#)

**AUTORES / AUTHORS:** - Moro MI; Manrique G; Uriarte R; Diaz L

**INSTITUCIÓN / INSTITUTION:** - Cathedra of Hematology, Hospital de Clinicas , Montevideo , Uruguay.

[255]

**TÍTULO / TITLE:** - Silencing HCCR2 expression inhibits the proliferation of leukemia cells by inducing apoptosis and promoting cell cycle arrest.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Dec;32(6):1373-9. doi: 10.3892/ijmm.2013.1518. Epub 2013 Oct 8.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1518](#)

**AUTORES / AUTHORS:** - Qiao SK; Ren HY; Shi YJ; Liu W

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Peking University First Hospital, Beijing 100034, P.R. China.

**RESUMEN / SUMMARY:** - The human cervical cancer oncogene (HCCR2) has been found to be overexpressed in a variety of human malignant tumors cells, and its function is related to cell cycle progression and survival. However, the molecular mechanisms of action of HCCR2 in leukemia remain unclear. In this study, we used the RNA interference strategy to investigate the effects of HCCR2 knockdown in the K562 leukemia cell line, and to explore the potential mechanisms involved. Following

transfection with small interfering RNA (siRNA) targeting HCCR2 (HCCR2-siRNA), we examined the effects of HCCR2 knockdown on cell morphology, cell proliferation, cell cycle progression and apoptosis in K562 cells. Morphological changes were evaluated by Wright-Giemsa staining. Cell cycle progression and apoptosis were measured by flow cytometry. The expression levels of genes related to the cell cycle and apoptosis were detected by quantitative RT-PCR (qRT-PCR) and western blot analysis. HCCR2 expression at the mRNA and protein level was significantly decreased following transfection with plasmids expressing HCCR2-siRNA. Silencing HCCR2 expression significantly suppressed cell proliferation, induced G1 cell cycle arrest and promoted the apoptosis of K562 cells. Additionally, we found that the expression of Bax, p53 and p21 was significantly increased, while Bcl-2 expression was significantly decreased in the HCCR2-siRNA-transfected cells. However, the expression of p27 was not affected. These results suggest that the HCCR2 gene plays an important role in the tumorigenesis of leukemia, thus making it an attractive therapeutic target for acute leukemia.

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[256]

**TÍTULO / TITLE:** - A phase I, dose-escalation study of cyclical weekly oral temozolomide and weekly PEG-interferon alpha-2b in patients with refractory or advanced solid tumours.

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

**REVISTA / JOURNAL:** - J Chemother. 2013 Jun 19.

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

[1179/1973947813Y.000000102](#)

**AUTORES / AUTHORS:** - Coker SA; Dandamudi UB; Beelen AP; Crosby NA; Fisher J; Obrocea M; Ernstoff MS; Lewis LD

**RESUMEN / SUMMARY:** - BACKGROUND: Temozolomide (TMZ) is an oral alkylating agent used in the treatment of central nervous system neoplasms and metastatic melanoma. Preclinical and clinical data suggested that combining TMZ with interferon alpha-2b (IFN-alpha-2b) may result in increased anti-tumour efficacy. METHODS: This was a phase I, dose-escalation study to define the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of cyclical oral TMZ (days 1-7 and 15-21) in combination with pegylated IFN-alpha-2b (PEG-IFN-alpha-2b) in patients with advanced solid tumours. RESULTS: We treated 19 patients (10 female and nine male), median age 58 years (range: 41-79 years). Ten patients tolerated TMZ at 100 mg/m<sup>2</sup> on days 1-7 and 15-21 plus PEG-IFN-alpha-2b at 1.5 mcg/kg/week on 28-day cycles which was the MTD of the combination. The pharmacokinetic parameters of PEG-IFN-alpha-2b were not altered by TMZ, at the MTD.

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[257]

**TÍTULO / TITLE:** - Co-expression of Rho guanine nucleotide exchange factor 5 and Src associates with poor prognosis of patients with resected non-small cell lung cancer.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2864-70. doi: 10.3892/or.2013.2797. Epub 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2797](#)

**AUTORES / AUTHORS:** - He P; Wu W; Wang H; Liao K; Zhang W; Xiong G; Wu F; Meng G; Yang K

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiothoracic Surgery, Southwest Hospital, Third Military Medical University, 400038 Chongqing, P.R. China.

**RESUMEN / SUMMARY:** - Specific and sensitive enough molecular biomarkers are lacking to accurately predict the survival of non-small cell lung cancer (NSCLC) patients. ARHGEF5 and Src have been shown to play an important role in tumorigenesis. However, the involvement of ARHGEF5 and Src in NSCLC remains unknown. Therefore, we evaluated the expression of ARHGEF5 and Src in resected NSCLC tissues and the correlation of co-expression of ARHGEF5 and Src and the prognosis of patients with resected NSCLC. Positive expression of ARHGEF5 was detected in 133 cases of 193 patients (68.91%). A total of 193 NSCLC patients (male: 145; female: 48; average age: 61.84 years; age range: 31-84) were enrolled in this study, of which 99 cases were squamous cell carcinomas (SCCs) (51.30%) and 94 cases were adenocarcinomas (ADCs) (48.70%). The expression of ARHGEF5 was mainly located in the cytoplasm of tumor cells, but not in the corresponding adjacent lung tissues. The levels of ARHGEF5 were significantly associated with age, differentiation and tumor stage. ARHGEF5 protein expression was associated with Src protein expression in NSCLC ( $\chi^2 = 11.874$ ,  $P < 0.01$ ) and in ADC ( $\chi^2 = 12.194$ ,  $P < 0.01$ ), but not in SCC. Co-immunoprecipitation revealed that there was a physical interaction between Src and ARHGEF5 in lung cancer cells. The patients with ARHGEF5(+)/Src(+) had a shorter survival time compared with the other patients (29.37 months versus 39.90 months,  $P = 0.029$ ). In conclusion, ARHGEF5/Src can be considered as a prognostic biomarker and a therapeutic target for patients with resected NSCLC.

[258]

**TÍTULO / TITLE:** - Prognostic/predictive value of 207 serum factors in colorectal cancer treated with cediranib and/or chemotherapy.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2765-73. doi: 10.1038/bjc.2013.649. Epub 2013 Oct 22.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.649](#)

**AUTORES / AUTHORS:** - Spencer SK; Pommier AJ; Morgan SR; Barry ST; Robertson JD; Hoff PM; Jurgensmeier JM

**INSTITUCIÓN / INSTITUTION:** - Clinical Oncology, AstraZeneca, Macclesfield, UK.

**RESUMEN / SUMMARY:** - Background: The prognostic and predictive value of multiple serum biomarkers was evaluated using samples from a randomised phase III study (HORIZON II) investigating chemotherapy with or without cediranib in metastatic colorectal cancer (mCRC). Methods: Baseline levels of 207 protein markers were measured in serum samples from 582 HORIZON II (FOLFOX/XELOX plus cediranib 20 mg (n=330) or placebo (n=252)) patients. Median baseline values of each biomarker were used to categorise patients as high or low. Markers were then assessed for their association with efficacy, defined by progression-free survival (PFS) and overall survival (OS). A generalised boosted regression model identified markers of particular interest. Results: Correlation of protein levels with PFS and OS suggested that multiple factors had a prognostic value, independent of treatment arm, including IL-6, IL-8, C-

reactive protein (CRP), ICAM-1 and carcinoembryonic antigen (CEA). Among the angiogenesis regulators, low levels of vascular endothelial growth factor (VEGF), VEGF-D, VEGFR-1, VEGFR-3, NRP1 and Tie-2 correlated with better outcome. Conclusion: This large data set generated using serum samples from mCRC patients treated with chemotherapy and VEGF inhibitors, defines baseline characteristics for 207 serum proteins. Multiple prognostic factors were identified that could be disease related or predict which patients derive most benefit from 5-fluorouracil (5-FU)-based chemotherapy, meriting further exploration in prospective studies.

[259]

**TÍTULO / TITLE:** - Increased TGF- $\alpha$  as a Mechanism of Acquired Resistance to the Anti-EGFR Inhibitor Cetuximab through EGFR-MET Interaction and Activation of MET Signaling in Colon Cancer Cells.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 14.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-](#)

[0423](#)

**AUTORES / AUTHORS:** - Troiani T; Martinelli E; Napolitano S; Vitagliano D; Ciuffreda LP; Costantino S; Morgillo F; Capasso A; Sforza V; Nappi A; De Palma R; D'Aiuto E; Berrino L; Bianco R; Ciardiello F

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Oncologia Medica and Immunologia Clinica, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale F. Magrassi e A. Lanzara; Sezione di Farmacologia, Dipartimento di Medicina Sperimentale, Seconda Università degli Studi di Napoli; and Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Università di Napoli Federico II, Naples, Italy.

**RESUMEN / SUMMARY:** - **PURPOSE:** Although cetuximab, an anti-EGF receptor (EGFR) monoclonal antibody, is an effective treatment for patients with KRAS wild-type metastatic colorectal cancer (mCRC), its clinical use is limited by onset of resistance. **EXPERIMENTAL DESIGN:** We characterized two colorectal cancer models to study the mechanisms of acquired resistance to cetuximab. **RESULTS:** Following chronic treatment of nude mice bearing cetuximab-sensitive human GEO colon xenografts, cetuximab-resistant GEO (GEO-CR) cells were obtained. In GEO-CR cells, proliferation and survival signals were constitutively active despite EGFR inhibition by cetuximab treatment. Whole gene expression profiling identified a series of genes involved in the hepatocyte growth factor (HGF)-MET-dependent pathways, which were upregulated in GEO-CR cells. Furthermore, activated, phosphorylated MET was detected in GEO-CR cells. A second colorectal cancer cell line with acquired resistance to cetuximab was obtained (SW48-CR). Inhibition of MET expression by siRNA restored cetuximab sensitivity in GEO-CR and SW48-CR cells, whereas exogenous activation of MET by HGF stimulation in cetuximab-sensitive GEO and SW48 cells induced resistance to cetuximab. Treatment of GEO-CR and SW48-CR cells with PHA665752, a selective MET inhibitor, inhibited cell growth, proliferation, and survival signals and impaired cancer cell migration. Overexpression of TGF- $\alpha$ , a specific EGFR ligand, was involved in the acquisition of cetuximab resistance in GEO-CR and SW48-CR cells. In fact, TGF- $\alpha$  overexpression induced the EGFR-

MET interaction, with subsequent MET phosphorylation and activation of MET downstream effectors in GEO-CR and SW48-CR cells. CONCLUSIONS: These results suggest that overexpression of TGF- $\alpha$  through induction of EGFR-MET interaction contributes to cetuximab resistance in colorectal cancer cells. The combined inhibition of EGFR and MET receptor could represent a strategy for preventing and/or overcoming cetuximab resistance in patients with colorectal cancer. Clin Cancer Res; 1-15. ©2013 AACR.

[260]

**TÍTULO / TITLE:** - Clinical applicability and prognostic significance of molecular response assessed by fluorescent-PCR of immunoglobulin genes in multiple myeloma. Results from a GEM/PETHEMA study.

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

**REVISTA / JOURNAL:** - Br J Haematol. 2013 Dec;163(5):581-9. doi: 10.1111/bjh.12576. Epub 2013 Oct 3.

•• Enlace al texto completo (gratis o de pago) [1111/bjh.12576](#)

**AUTORES / AUTHORS:** - Martínez-Lopez J; Fernández-Redondo E; García-Sanz R; Montalbán MA; Martínez-Sánchez P; Pavia B; Mateos MV; Rosinol L; Martín M; Ayala R; Martínez R; Blanchard MJ; Alegre A; Besalduch J; Bargay J; Hernández MT; Sarasquete ME; Sánchez-Godoy P; Fernández M; Blade J; San Miguel JF; Lahuerta JJ

**INSTITUCIÓN / INSTITUTION:** - Servicio de Hematología & Instituto de Investigación, Hospital Universitario 12 de Octubre, Madrid, España.

**RESUMEN / SUMMARY:** - Minimal residual disease monitoring is becoming increasingly important in multiple myeloma (MM), but multiparameter flow cytometry (MFC) and allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) techniques are not routinely available. This study investigated the prognostic influence of achieving molecular response assessed by fluorescent-PCR (F-PCR) in 130 newly diagnosed MM patients from Grupo Español Multidisciplinar de Melanoma (GEM)2000/GEM05 trials (NCT00560053, NCT00443235, NCT00464217) who achieved almost very good partial response after induction therapy. As a reference, we used the results observed with simultaneous MFC. F-PCR at diagnosis was performed on DNA using three different multiplex PCRs: IGH D-J, IGK V-J and KDE rearrangements. The applicability of F-PCR was 91.5%. After induction therapy, 64 patients achieved molecular response and 66 non-molecular response; median progression-free survival (PFS) was 61 versus 36 months, respectively ( $P = 0.001$ ). Median overall survival (OS) was not reached (NR) in molecular response patients (5-year survival: 75%) versus 66 months in the non-molecular response group ( $P = 0.03$ ). The corresponding PFS and OS values for patients with immunophenotypic versus non-immunophenotypic response were 67 versus 42 months ( $P = 0.005$ ) and NR (5-year survival: 95%) versus 69 months ( $P = 0.004$ ), respectively. F-PCR analysis is a rapid, affordable, and easily performable technique that, in some circumstances, may be a valid approach for minimal residual disease investigations in MM.

[261]

**TÍTULO / TITLE:** - KRAS mutation confers resistance to antibody-dependent cellular cytotoxicity of cetuximab against human colorectal cancer cells.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 18. doi: 10.1002/ijc.28550.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28550](#)

**AUTORES / AUTHORS:** - Nakadate Y; Kodera Y; Kitamura Y; Shirasawa S; Tachibana T; Tamura T; Koizumi F

**INSTITUCIÓN / INSTITUTION:** - Shien-Lab, National Cancer Center Hospital, Tokyo, Japan; Department of Bioengineering, Graduate School of Engineering, Osaka City University, Osaka, Japan.

**RESUMEN / SUMMARY:** - Cetuximab is a chimeric IgG1 monoclonal antibody (mAb) that targets the extracellular domain of epidermal growth factor receptor (EGFR). Oncogenic KRAS mutations in tumors have been shown to be a negative predictor of the response of colorectal cancer (CRC) to cetuximab treatment. Cetuximab exerts its therapeutic effects through several mechanisms including antibody-dependent cellular cytotoxicity (ADCC). However, the influence of KRAS mutations on cetuximab-mediated ADCC is not fully understood. Here, we investigated cetuximab-mediated ADCC in two pairs of isogenic CRC cells with or without a KRAS mutation. Peripheral blood mononuclear cells (PBMCs) from healthy volunteers and NK92, a natural killer (NK) cell line that exogenously expresses FcγRIIIa (CD16a), were used as effector cells. In an ADCC assay, perforin-dependent target cell lysis was not affected by the KRAS mutation status. On the other hand, perforin-independent ADCC was observed only in CRC cells with wild-type KRAS, but not in cells with mutant KRAS. Neutralizing experiments revealed that the Fas-Fas ligand (FasL) interaction was responsible for the induction of apoptosis and perforin-independent ADCC. Furthermore, the presence of effector cells clearly enhanced the growth-inhibitory effect of cetuximab only in CRC cells with wild-type KRAS, but not in those with mutant KRAS. These findings suggest that ADCC is an important mode of action of cetuximab and that KRAS mutation impairs the therapeutic effect exerted by cetuximab-mediated ADCC. © 2013 Wiley Periodicals, Inc.

[262]

**TÍTULO / TITLE:** - Bevacizumab-induced vessel normalization hampers tumor uptake of antibodies—response.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Dec 1;73(23):7147-8. doi: 10.1158/0008-5472.CAN-13-2532. Epub 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-2532](#)

**AUTORES / AUTHORS:** - Arjaans M; Oosting SF; Schroder CP; de Vries EG

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliation: Department of Medical Oncology, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands.

[263]

**TÍTULO / TITLE:** - The Janus Kinases Inhibitor AZD1480 Attenuates Growth of Small Cell Lung Cancers In Vitro and In Vivo.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1110](https://doi.org/10.1158/1078-0432.CCR-13-1110)

**AUTORES / AUTHORS:** - Lee JH; Park KS; Alberobello AT; Kallakury B; Weng MT; Wang Y; Giaccone G

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and Lombardi Comprehensive Cancer Center, Georgetown University, Washington, District of Columbia.

**RESUMEN / SUMMARY:** - PURPOSE: The prognosis of small cell lung cancer (SCLC) is poor, and there has been very little progress in the medical treatment of SCLC in the past two decades. We investigated the potential of Janus-activated kinases (JAK) inhibitor, AZD1480, for treatment of SCLC in vitro and in vivo. EXPERIMENTAL DESIGN: JAK1 and JAK2 were inhibited by AZD1480 or siRNAs, and the effect of inhibition of JAK gene family on SCLC cell viability was evaluated. The effect of AZD1480 on cell-cycle distribution and apoptosis induction was studied. Antitumor effects of AZD1480 in tumor xenografts were assessed. RESULTS: AZD1480 significantly inhibited growth of six out of 13 SCLC cells with IC50s ranging from 0.73 to 3.08  $\mu\text{mol/L}$ . Knocking down of JAK2 and JAK1 inhibited proliferation of Jak2-positive/Jak1-negative H82 cells and Jak1-positive/Jak2-negative GLC4 cells, respectively. Treatment of SCLC cells with AZD1480 for 24 hours resulted in an increase of 4N DNA content and histone 3 serine 10 phosphorylation, indicative of G2-M phase arrest. Moreover, SCLCs underwent apoptosis after AZD1480 treatment as exemplified by the downregulation of MCL1, the accumulation of cleaved caspase 3, cleaved PARP, and increase of annexin-V-positive cells. Finally, xenograft experiments showed that AZD1480 attenuated the growth of H82 and GLC4 tumors in mice, and we observed stronger apoptosis as well as decreased CD31-positive endothelial cells in H82 and GLC4 xenografts upon AZD1480 treatment. CONCLUSIONS: JAK inhibitor AZD1480 attenuated growth of SCLC cells in vitro and in vivo. Clinical development of anti-JAKs therapies in SCLC warrants further investigation. Clin Cancer Res; 19(24); 1-10. ©2013 AACR.

[264]

**TÍTULO / TITLE:** - A novel synthetic analog of militarin, MA-1 induces mitochondrial dependent apoptosis by ROS generation in human lung cancer cells.

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

**REVISTA / JOURNAL:** - Toxicol Appl Pharmacol. 2013 Oct 22. pii: S0041-008X(13)00463-8. doi: 10.1016/j.taap.2013.10.015.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.10.015](https://doi.org/10.1016/j.taap.2013.10.015)

**AUTORES / AUTHORS:** - Yoon DH; Lim MH; Lee YR; Sung GH; Lee TH; Jeon BH; Cho JY; Song WO; Park H; Choi S; Kim TW

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea.

**RESUMEN / SUMMARY:** - A synthetic Militarin analog-1[(2R,3R,4R,5R)-1,6-bis(4-(2,4,4-trimethylpentan-2-yl)phenoxy) hexane-2,3,4,5-tetraol] is a novel derivative of constituents from Cordyceps militaris, which has been used to treat a variety of chronic diseases including inflammation, diabetes, hyperglycemia and cancers. Here, we report

for the first time the synthesis of Militarín analog-1 (MA-1) and the apoptotic mechanism of MA-1 against human lung cancer cell lines. Treatment with MA-1 significantly inhibited the viability of 3 human lung cancer cell lines. The inhibition of viability and growth in MA-1-treated A549 cells with an IC<sub>50</sub> of 5 μM were mediated through apoptosis induction, as demonstrated by an increase in DNA fragmentation, sub-G<sub>0</sub>/G<sub>1</sub>-DNA fraction, nuclear condensation, and phosphatidylserine exposure. The apoptotic cell death caused mitochondrial membrane permeabilization through regulation of expression of the Bcl-2 family proteins, leading to cytochrome c release in a time-dependent manner. Subsequently, the final stage of apoptosis, activation of caspase-9/-3 and cleavage of poly (ADP ribose) polymerase, was induced. Furthermore, A549 lung cancer cells were more responsive to MA-1 than a bronchial epithelial cell line (BEAS-2B), involving the rapid generation of reactive oxygen species (ROS), c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) activation. The pharmacological inhibition of ROS generation and JNK/p38 MAPK exhibited attenuated DNA fragmentation in MA-1-induced apoptosis. Oral administration of MA-1 also retarded growth of A549 orthotopic xenografts. In conclusion, the present study indicates that the new synthetic derivative MA-1 triggers mitochondrial apoptosis through ROS generation and regulation of MAPKs and may be a potent therapeutic agent against human lung cancer.

[265]

**TÍTULO / TITLE:** - Synthesis of novel 2-cyano substituted glycyrrhetic acid derivatives as inhibitors of cancer cells growth and NO production in LPS-activated J-774 cells.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem. 2013 Nov 7. pii: S0968-0896(13)00923-1. doi: 10.1016/j.bmc.2013.10.049.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmc.2013.10.049](#)

**AUTORES / AUTHORS:** - Salomatina OV; Markov AV; Logashenko EB; Korchagina DV; Zenkova MA; Salakhutdinov NF; Vlassov VV; Tolstikov GA

**INSTITUCIÓN / INSTITUTION:** - N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch Russian Academy of Sciences, 9, Lavrentiev ave., Novosibirsk 630090, Russian Federation.

**RESUMEN / SUMMARY:** - Here we report the synthesis and biological activity of new semi-synthetic derivatives of naturally occurring glycyrrhetic acid bearing a 2-cyano-3-oxo-1-en moiety in the A-ring and double bonds and carbonyl groups in the C, D and E rings. Bioassays using murine macrophage-like and tumor cells show that compound 4, which differs from Soloxolone methyl by the absence of a 9(11)-double bond in the C-ring, displays anti-inflammatory and inhibitory activities with respect to tumor cells with a high selectivity index value.

[266]

**TÍTULO / TITLE:** - An intact immune system is required for the anti-cancer activities of histone deacetylase inhibitors.

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

**REVISTA / JOURNAL:** - Cancer Res. 2013 Oct 24.

- Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-0890](#)

**AUTORES / AUTHORS:** - West AC; Mattarollo SR; Shortt J; Cluse LA; Christiansen AJ; Smyth MJ; Johnstone RW

**INSTITUCIÓN / INSTITUTION:** - Cancer Therapeutics Program, Peter McCallum Cancer Centre.

**RESUMEN / SUMMARY:** - Cell-intrinsic effects such as induction of apoptosis and/or inhibition of cell proliferation have been proposed as the major anti-tumor responses to histone deacetylase inhibitors (HDACi). These compounds can also mediate immunomodulatory effects that may also contribute to their anti-cancer effects. However, HDACi can also induce anti-inflammatory, and potentially immunosuppressive, outcomes. We therefore sought to clarify the role of the immune system in mediating the efficacy of HDACi in a physiological setting, utilizing pre-clinical, syngeneic murine models of haematological malignancies and solid tumors. We showed an intact immune system was required for the robust anti-cancer effects of the HDACi vorinostat and panobinostat against a colon adenocarcinoma and two aggressive models of leukemia/lymphoma. Importantly, while HDACi-treated immunocompromised mice bearing established lymphoma succumbed to disease significantly earlier than tumor-bearing, HDACi-treated wild type mice, treatment with the conventional chemotherapeutic etoposide equivalently enhanced the survival of both strains. IFN-gamma and tumor cell signaling through IFN-gammaR were particularly important for the anti-cancer effects of HDACi, and vorinostat and IFN-gamma acted in concert to enhance the immunogenicity of tumor cells. Furthermore, we show that a combination of vorinostat with alpha-GalCer, an IFN-gamma-inducing agent, was significantly more potent against established lymphoma than vorinostat treatment alone. Intriguingly, B cells, but not NK cells or CD8+ T cells, were implicated as effectors of the vorinostat anti-tumor immune response. Together our data suggests HDACi are immunostimulatory during cancer treatment and that combinatorial therapeutic regimes with immunotherapies should be considered in the clinic.

[267]

**TÍTULO / TITLE:** - SOX2 regulates apoptosis through MAP4K4-Survivin signaling pathway in human lung cancer cells.

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

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 Nov 14.

- Enlace al texto completo (gratis o de pago) [1093/carcin/bgt371](#)

**AUTORES / AUTHORS:** - Chen S; Li X; Lu D; Xu Y; Mou W; Wang L; Chen Y; Liu Y; Li X; Li LY; Liu L; Stupack D; Reisfeld RA; Xiang R; Li N

**INSTITUCIÓN / INSTITUTION:** - School of Medicine, Nankai University, 94 Weijin Road, Tianjin, China 300071.

**RESUMEN / SUMMARY:** - Previous studies have implicated cancer stem cells in tumor recurrence, and revealed that the stem cell gene-SOX2 plays an important role in the tumor cell resistance to apoptosis. Nonetheless, the mechanism by which SOX2 regulates apoptosis signals remained undefined. Here, we demonstrated the surprising finding that silencing of the SOX2 gene effectively induces apoptosis via the activation of death receptor and mitochondrial signaling pathways in human non-small cell lung cancer (NSCLC) cells. Unexpectedly, RT-PCR analysis suggested that down-

regulation of SOX2 leads to activation of MAP4K4, previously implicated in cell survival. Evaluation of the apoptotic pathways revealed an increased expression of key inducers of apoptosis, including TNF-alpha and p53, with concurrent attenuation of Survivin. While p53 appeared dispensable for this pathway, the loss of Survivin in SOX2 deficient cells appeared critical for the observed MAP4K4 induced cell death. Rescue experiments revealed that SOX2 silencing mediated killing was blocked by ectopic expression of Survivin, or by reduction of MAP4K4 expression. Clinically, expression of Survivin and SOX2 were highly correlated with each other and with poor outcome. The results reveal a key target of SOX2 expression and highlight the unexpected context-dependent role for MAP4K4, a pluripotent activator of several MAPK pathways, in regulating tumor cell survival.

[268]

**TÍTULO / TITLE:** - Heat-shock protein 90 inhibitors synergistically enhance melanoma differentiation-associated gene-7-mediated cell killing of human pancreatic carcinoma.

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

**REVISTA / JOURNAL:** - Cancer Gene Ther. 2013 Nov 22. doi: 10.1038/cgt.2013.66.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cgt.2013.66](#)

**AUTORES / AUTHORS:** - Zhang Z; Kawamura K; Jiang Y; Shingyoji M; Ma G; Li Q; Hu J; Qi Y; Liu H; Zhang F; Kang S; Shan B; Wang S; Chada S; Tagawa M

**INSTITUCIÓN / INSTITUTION:** - [1] Division of Pathology and Cell Therapy, Chiba Cancer Center Research Institute, Chuo-ku, Chiba, Japan [2] Department of Gynecology and Obstetrics, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China.

**RESUMEN / SUMMARY:** - Pancreatic cancer is one of the intractable diseases and an effective therapeutic strategy is required to improve the prognosis. We examined possible antitumor effects of adenoviruses expressing melanoma differentiation-associated gene-7/interleukin-24 (Ad-mda-7) and a heat-shock protein 90 (Hsp90) inhibitor to human pancreatic carcinoma cells. Ad-mda-7 and an Hsp90 inhibitor, geldanamycin (GA), produced cytotoxic effects, and a combinatory use of Ad-mda-7 and GA further achieved synergistic effects. Administration of N-acetyl-L-cysteine, an inhibitor of reactive oxygen species, eliminated Ad-mda-7- and GA-mediated cytotoxicity. Ad-mda-7 augmented phosphorylated AKT levels but GA did not influence the phosphorylation. GA-treated cells showed cleavage of poly-(ADP-ribose) polymerase but not caspase-3, and upregulated Hsp70 and LC3A/B II levels, whereas Ad-mda-7-treated cells did not. GA treatments augmented ubiquitination and markedly increased melanoma differentiation-associated gene-7 (MDA-7) expression levels. These findings suggest that Ad-mda-7-mediated cytotoxicity is dependent on reactive oxygen species but independent of apoptosis or autophagy, and that GA-mediated cytotoxicity was linked with caspase-independent apoptosis and/or autophagy. A mechanism underlying the combinatory effects of Ad-mda-7 and GA remained complex and the synergism is attributable to multiple factors including increased MDA-7 protein stability by GA. Cancer Gene Therapy advance online publication, 22 November 2013; doi:10.1038/cgt.2013.66.

[269]

**TÍTULO / TITLE:** - Prediction of peritoneal recurrence by the mRNA level of CEA and MMP-7 in peritoneal lavage of gastric cancer patients.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 27.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1458-8](http://1007/s13277-013-1458-8)

**AUTORES / AUTHORS:** - Li Z; Zhang D; Zhang H; Miao Z; Tang Y; Sun G; Dai D

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, 4<sup>th</sup> Affiliated Hospital of China Medical University, Shenyang, Liaoning, 110032, China.

**RESUMEN / SUMMARY:** - A number of tumor markers had been reported to be useful in detecting free cancer cells in the peritoneal cavity and predict peritoneal recurrence in gastric cancer patients. The objective of this study was to compare the clinical impact of different tumor markers in peritoneal lavage fluid using the real-time quantitative reverse transcription polymerase chain reaction (RT-PCR) technique and to screen the most effective ones from them. The peritoneal lavage fluid of 116 patients with gastric cancer was sampled at laparotomy. After RNA extraction and reverse transcription, real-time quantitative polymerase chain reaction (PCR) was performed using the primers and probes for carcinoembryonic antigen (CEA), cytokeratin-20, matrix metalloproteinase-7 (MMP-7), carbohydrate antigen 125, and transforming growth factor-beta-1. Among the 116 patients, 45 (38.8 %) were confirmed to have peritoneal recurrence. Any of the PCR-positive results of the five tumor markers could predict peritoneal recurrence in the univariate analysis ( $P < 0.001$ ). In the multivariate analysis, the PCR results of CEA ( $P = 0.003$ ) and MMP-7 ( $P = 0.028$ ) were found to be independent prognostic factors. A real-time quantitative RT-PCR analysis of the CEA and MMP-7 transcripts in peritoneal lavage fluid could effectively predict peritoneal recurrence in advanced gastric cancer patients who underwent a potentially curative resection.

[270]

**TÍTULO / TITLE:** - Discovery of chemotherapy-associated ovarian cancer antigens by interrogating memory T cells.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 6. doi: 10.1002/ijc.28515.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28515](http://1002/ijc.28515)

**AUTORES / AUTHORS:** - Paroli M; Bellati F; Videtta M; Focaccetti C; Mancone C; Donato T; Antonilli M; Perniola G; Accapezzato D; Napoletano C; Nuti M; Bartolazzi A; Panici PB; Tripodi M; Palombo F; Barnaba V

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Scienze e Biotechnologie Medico-Chirurgiche, Sapienza Università di Roma, Rome, Italy.

**RESUMEN / SUMMARY:** - According to the immunogenic cell death hypothesis, clinical chemotherapy treatments may result in CD8+ and CD4+ T-cell responses against tumor cells. To discover chemotherapy-associated antigens (CAAs), T cells derived from ovarian cancer (OC) patients (who had been treated with appropriate chemotherapy protocols) were interrogated with proteins isolated from primary OC cells. We screened for immunogenicity using two-dimensional electrophoresis gel-eluted OC proteins. Only the selected immunogenic antigens were molecularly characterized by mass-spectrometry-based analysis. Memory T cells that recognized antigens associated with apoptotic (but not live) OC cells were correlated with

prolonged survival in response to chemotherapy, supporting the model of chemotherapy-induced apoptosis as an adjuvant of anti-tumor immunity. The strength of both memory CD4+ and CD8+ T cells producing either IFN-gamma or IL-17 in response to apoptotic OC antigens was also significantly greater in Responders to chemotherapy than in nonresponders. Immunogenicity of some of these antigens was confirmed using recombinant proteins in an independent set of patients. The T-cell interrogation system represents a strategy of reverse tumor immunology that proposes to identify CAAs, which may then be validated as possible prognostic tumor biomarkers or cancer vaccines.

[271]

**TÍTULO / TITLE:** - Epithelial splicing regulatory protein 1 is a favorable prognostic factor in pancreatic cancer that attenuates pancreatic metastases.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Sep 30. doi: 10.1038/onc.2013.392.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.392](#)

**AUTORES / AUTHORS:** - Ueda J; Matsuda Y; Yamahatsu K; Uchida E; Naito Z; Korc M; Ishiwata T

**INSTITUCIÓN / INSTITUTION:** - [1] Departments of Pathology and Integrative Oncological Pathology, Nippon Medical School, Tokyo, Japan [2] Department of Surgery for Organ and Biological Regulation, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan.

**RESUMEN / SUMMARY:** - Epithelial splicing regulatory protein 1 (ESRP1) binds the FGFR-2 auxiliary cis-element ISE/ISS-3, located in the intron between exon IIIb and IIIc, and primarily promotes FGFR-2 IIIb expression. Here we assessed the role of ESRP1 in pancreatic ductal adenocarcinoma (PDAC). Immunohistochemical analysis was performed using anti-ESRP1, FGFR-2 IIIb and FGFR-2 IIIc antibodies in 123 PDAC cases. ESRP1 expression vector and small interference RNA (siRNA) targeting ESRP1 were transfected into human PDAC cells, and cell growth, migration and invasion were analyzed. In vivo heterotopic and orthotopic implantations using ESRP1 overexpression clones were performed and effects on pancreatic tumor volumes and hepatic and pulmonary metastases determined. ESRP1 immunoreactivity was strong in the nuclei of cancer cells in well-to-moderately differentiated PDACs but weak in poorly differentiated cancers. Well-to-moderately differentiated cancers also exhibited high FGFR-2 IIIb and low FGFR-2 IIIc expression, whereas this ratio was reversed in the poorly differentiated cancers. Increased ESRP1 expression was associated with longer survival in comparison with low ESRP1 expression, and PANC-1 cells engineered to express ESRP1 exhibited increased FGFR-2 IIIb expression and decreased migration and invasion in vitro, whereas ESRP1 siRNA-transfected KLM-1 cells exhibited increased FGFR-2 IIIc expression and increased cell growth, migration and invasion. In vivo, ESRP1-overexpressing clones formed significantly fewer liver metastases as compared with control clones. ESRP1 regulates the expression pattern of FGFR-2 isoforms, attenuates cell growth, migration, invasion and metastasis, and is a favorable prognostic factor in PDAC. Therefore, devising mechanisms to upregulate ESRP1 may exert a beneficial therapeutic effect in PDAC. Oncogene advance online publication, 30 September 2013; doi:10.1038/onc.2013.392.

[272]

**TÍTULO / TITLE:** - Etoposide induces apoptosis via the mitochondrial- and caspase-dependent pathways and in non-cancer stem cells in Panc-1 pancreatic cancer cells.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2765-70. doi: 10.3892/or.2013.2767. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2767](#)

**AUTORES / AUTHORS:** - Zhang SH; Huang Q

**INSTITUCIÓN / INSTITUTION:** - Experimental Research Center, First People's Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200080, P.R. China.

**RESUMEN / SUMMARY:** - Pancreatic cancer is a highly aggressive malignant tumor. In the present study, we performed several methods, including CCK-8 assay, immunofluorescence technique, western blotting and flow cytometry, to determine the effects of VP16 (etoposide) on Panc-1 pancreatic cancer cells. The results demonstrated that VP16 inhibited the growth of and induced apoptosis in Panc-1 cells. Western blot analysis showed that VP16 inhibited the expression of Bcl-2 and enhanced the expression of Bax, caspases-3 and -9, cytochrome c and PARP. Notably, a strong inhibitory effect of VP16 on Panc-1 cells mainly occurred in non-CSCs. These data provide a new strategy for the therapy of pancreatic cancer.

[273]

**TÍTULO / TITLE:** - Tumor Necrosis Factor-Alpha and Apoptosis Induction in Melanoma Cells through Histone Modification by 3-Deazaneplanocin A.

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

**REVISTA / JOURNAL:** - J Invest Dermatol. 2013 Nov 13. doi: 10.1038/jid.2013.489.

●● Enlace al texto completo (gratis o de pago) [1038/jid.2013.489](#)

**AUTORES / AUTHORS:** - Tanaka R; Donovan N; Yu Q; Irie R; Hoon DS

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Oncology, Santa Monica, CA, USA.

[274]

**TÍTULO / TITLE:** - Triptolide-induced Cell Death in Pancreatic Cancer Is Mediated by O-GlcNAc Modification of Transcription Factor Sp1.

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

**REVISTA / JOURNAL:** - J Biol Chem. 2013 Nov 22;288(47):33927-38. doi: 10.1074/jbc.M113.500983. Epub 2013 Oct 15.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.500983](#)

**AUTORES / AUTHORS:** - Banerjee S; Sangwan V; McGinn O; Chugh R; Dudeja V; Vickers SM; Saluja AK

**INSTITUCIÓN / INSTITUTION:** - From the Division of Basic and Translational Research, Department of Surgery, and.

**RESUMEN / SUMMARY:** - Pancreatic cancer, the fourth most prevalent cancer-related cause of death in the United States, is a disease with a dismal survival rate of 5% 5 years after diagnosis. One of the survival proteins responsible for its extraordinary ability to evade cell death is HSP70. A naturally derived compound, triptolide, and its

water-soluble prodrug, Minnelide, down-regulate the expression of this protein in pancreatic cancer cells, thereby causing cell death. However, the mechanism of action of triptolide has not been elucidated. Our study shows that triptolide-induced down-regulation of HSP70 expression is associated with a decrease in glycosylation of the transcription factor Sp1. We further show that triptolide inhibits glycosylation of Sp1, inhibiting the hexosamine biosynthesis pathway, particularly the enzyme O-GlcNAc transferase. Inhibition of O-GlcNAc transferase prevents nuclear localization of Sp1 and affects its DNA binding activity. This in turn down-regulates prosurvival pathways like NF-kappaB, leading to inhibition of HSF1 and HSP70 and eventually to cell death. In this study, we evaluated the mechanism by which triptolide affects glycosylation of Sp1, which in turn affects downstream pathways controlling survival of pancreatic cancer cells.

[275]

**TÍTULO / TITLE:** - Increased killing of SCCVII squamous cell carcinoma cells after the combination of Pc 4 photodynamic therapy and dasatinib is associated with enhanced caspase-3 activity and ceramide synthase 1 upregulation.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):2064-72. doi: 10.3892/ijo.2013.2132. Epub 2013 Oct 9.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2132](#)

**AUTORES / AUTHORS:** - Separovic D; Breen P; Boppana NB; Van Buren E; Joseph N; Kravicka JM; Rahmaniyan M; Li L; Guduz TI; Bielawska A; Bai A; Bielawski J; Pierce JS; Korbelik M

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI 48201, USA.

**RESUMEN / SUMMARY:** - Photodynamic therapy (PDT) is not always effective as an anticancer treatment, therefore, PDT is combined with other anticancer agents for improved efficacy. The combination of dasatinib and PDT with the silicone phthalocyanine photosensitizer Pc 4 was assessed for increased killing of SCCVII mouse squamous cell carcinoma cells, a preclinical model of head and neck squamous cell carcinoma, using apoptotic markers and colony formation as experimental end-points. Because each of these treatments regulates the metabolism of the sphingolipid ceramide, their effects on mRNA levels of ceramide synthase, a ceramide-producing enzyme, and the sphingolipid profile were determined. PDT + dasatinib induced an additive loss of clonogenicity. Unlike PDT alone or PDT + dasatinib, dasatinib induced zVAD-fmk-dependent cell killing. PDT or dasatinib-induced caspase-3 activation was potentiated after the combination. PDT alone induced mitochondrial depolarization, and the effect was inhibited after the combination. Annexin V+ and propidium iodide+ cells remained at control levels after treatments. In contrast to PDT alone, dasatinib induced upregulation of ceramide synthase 1 mRNA, and the effect was enhanced after the combination. Dasatinib induced a modest increase in C20:1- and C22-ceramide but had no effect on total ceramide levels. PDT increased the levels of 12 individual ceramides and total ceramides, and the addition of dasatinib did not affect these increases. PDT alone decreased substantially sphingosine levels and inhibited the activity of acid ceramidase, an enzyme that

converts ceramide to sphingosine. The data suggest that PDT-induced increases in ceramide levels do not correlate with ceramide synthase mRNA levels but rather with inhibition of ceramidase. Cell killing was zVAD-fmk-sensitive after dasatinib but not after either PDT or the combination and enhanced cell killing after the combination correlated with potentiated caspase-3 activation and upregulation of ceramide synthase 1 mRNA but not the production of ceramide. The data imply potential significance of the combination for cancer treatment.

[276]

**TÍTULO / TITLE:** - HRAS mutations and resistance to the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in head and neck squamous cell carcinoma cells.

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

**REVISTA / JOURNAL:** - Head Neck. 2013 Sep 30. doi: 10.1002/hed.23499.

●● [Enlace al texto completo \(gratis o de pago\) 1002/hed.23499](#)

**AUTORES / AUTHORS:** - Hah JH; Zhao M; Pickering CR; Frederick MJ; Andrews GA; Jasser SA; Fooshee DR; Milas ZL; Galer C; Sano D; William WN Jr; Kim E; Heymach J; Byers LA; Papadimitrakopoulou V; Myers JN

**INSTITUCIÓN / INSTITUTION:** - Departments of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Otolaryngology-Head and Neck Surgery, Seoul National University Hospital and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - Background: This was to identify mechanisms of innate resistance to an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, in a panel of head and neck squamous cell carcinoma (HNSCC) cell lines. Specifically, we analyzed the role of HRAS mutations in erlotinib resistance. Methods: Erlotinib sensitivity was determined by MTT assays. Molecular signaling pathways and somatic mutations were examined. Changes in sensitivity after modulation of HRAS expression were evaluated. Results: All seven cell lines were wild-type for EGFR and KRAS regardless of erlotinib sensitivity; however, one erlotinib-resistant cell line (HN31) harbored an HRAS G12D mutation. Down regulation of HRAS expression by siRNA or shRNA in HN31 led to increased erlotinib sensitivity in vitro and in vivo. Transfection of activating HRAS-mutant (G12D and G12V) constructs into erlotinib-sensitive cell lines made them more resistant to erlotinib. Conclusion: Activating HRAS mutations can confer erlotinib resistance in an HRAS mutant HNSCC cell line. Head Neck, 2013.

[277]

**TÍTULO / TITLE:** - Human Pancreatic Cancer Cells with Acquired Gemcitabine Resistance Exhibit Significant Up-regulation of Peroxiredoxin-2 Compared to Sensitive Parental Cells.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):4821-6.

**AUTORES / AUTHORS:** - Suenaga S; Kuramitsu Y; Wang Y; Baron B; Kitagawa T; Akada J; Tokuda K; Kaino S; Maehara S; Maehara Y; Sakaida I; Nakamura K

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Functional Proteomics, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. [climates@yamaguchi-u.ac.jp](mailto:climates@yamaguchi-u.ac.jp).

**RESUMEN / SUMMARY:** - Gemcitabine (2'-deoxy-2'-difluorodeoxycytidine) is the only clinically effective drug for pancreatic cancer. However, high levels of inherent and acquired tumor resistance to gemcitabine lead to difficulty of chemotherapy for pancreatic cancer. We have reported on a proteomic study of gemcitabine-sensitive KLM1 and -resistant KLM1-R pancreatic cancer cells, and identified some proteins which were shown to be up-regulated in KLM1-R compared to KLM1 cells. In those proteomic studies, peroxiredoxin-2 was listed as an up-regulated protein in KLM1-R cells. Peroxiredoxin-2 is a member of a family of peroxiredoxins providing a protective role for redox damage. In this study, the expression of peroxiredoxin-2 in KLM1 and KLM1-R cells was compared. It was found that peroxiredoxin-2 was significantly up-regulated in KLM1-R cells compared to KLM1 cells ( $p < 0.001$ ). However, peroxiredoxin-1 expression was significantly down-regulated in KLM1-R cells ( $p < 0.001$ ). These results suggest that peroxiredoxin-2 is a possible candidate biomarker for predicting the response of patients with pancreatic cancer to treatment with gemcitabine.

[278]

**TÍTULO / TITLE:** - miR-181b promotes cell proliferation and reduces apoptosis by repressing the expression of adenylyl cyclase 9 (AC9) in cervical cancer cells.

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

**REVISTA / JOURNAL:** - FEBS Lett. 2013 Nov 20. pii: S0014-5793(13)00853-3. doi: 10.1016/j.febslet.2013.11.019.

●● Enlace al texto completo (gratis o de pago) [1016/j.febslet.2013.11.019](http://1016/j.febslet.2013.11.019)

**AUTORES / AUTHORS:** - Yang L; Wang YL; Liu S; Zhang PP; Chen Z; Liu M; Tang H

**INSTITUCIÓN / INSTITUTION:** - Tianjin Life Science Research Center, Department of Microbiology, School of Basic Medical Sciences, Tianjin Medical University, Tianjin, China.

**RESUMEN / SUMMARY:** - MicroRNAs are a class of small, endogenous, non-coding RNAs that function as post-transcriptional regulators. In this study, we found that miR-181b promoted cell proliferation and inhibited cell apoptosis in cervical cancer cells. And we validated a new miR-181b target gene, adenylyl cyclase 9 (AC9). miR-181b restricted cAMP production by post-transcriptionally downregulating AC9 expression. Phenotypic experiments indicated that miR-181b and AC9 exerted opposite effects on cell proliferation and apoptosis.

[279]

**TÍTULO / TITLE:** - Transcriptional and post-translational regulation of Bim controls apoptosis in melatonin-treated human renal cancer Caki cells.

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

**REVISTA / JOURNAL:** - J Pineal Res. 2013 Oct 12. doi: 10.1111/jpi.12102.

●● Enlace al texto completo (gratis o de pago) [1111/jpi.12102](http://1111/jpi.12102)

**AUTORES / AUTHORS:** - Park EJ; Woo SM; Min KJ; Kwon TK

**INSTITUCIÓN / INSTITUTION:** - Department of Immunology, School of Medicine, Keimyung University, Daegu, Korea.

**RESUMEN / SUMMARY:** - Melatonin (N-acetyl-5-methoxytryptamine) has recently gained attention as an anticancer agent and for combined cancer therapy. In this study, we investigated the underlying molecular mechanisms of the effects of melatonin on cancer cell death. Treatment with melatonin induced apoptosis and upregulated the expression of the pro-apoptotic protein Bcl-2-interacting mediator of cell death (Bim) in renal cancer Caki cells. Furthermore, downregulation of Bim expression by siRNA markedly reduced melatonin-mediated apoptosis. Melatonin increased Bim mRNA expression through the induction of Sp1 and E2F1 expression and transcriptional activity. We found that melatonin also modulated Bim protein stability through the inhibition of proteasome activity. However, melatonin-induced Bim upregulation was independent of melatonin's antioxidant properties and the melatonin receptor. Taken together, our results suggest that melatonin induces apoptosis through the upregulation of Bim expression at the transcriptional level and at the post-translational level.

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[280]

**TÍTULO / TITLE:** - Sequential use of mammalian target of rapamycin inhibitors in patients with metastatic renal cell carcinoma following failure of tyrosine kinase inhibitors.

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

**REVISTA / JOURNAL:** - Med Oncol. 2013 Dec;30(4):745. doi: 10.1007/s12032-013-0745-y. Epub 2013 Oct 13.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0745-y](#)

**AUTORES / AUTHORS:** - Kumano M; Miyake H; Harada K; Fujisawa M

**INSTITUCIÓN / INSTITUTION:** - Division of Urology, Kobe University Graduate School of Medicine, Kobe, Japan.

**RESUMEN / SUMMARY:** - The aim of the study is to evaluate the clinical experience of the sequential use of mammalian target of rapamycin inhibitors (mTORIs) for metastatic renal cell carcinoma (mRCC) refractory to tyrosine kinase inhibitors (TKIs). This study retrospectively investigated the clinical outcomes in a total of 83 consecutive Japanese patients with mRCC who were treated with either everolimus or temsirolimus following the failure of sorafenib and/or sunitinib. Of the 83 patients, 15, 61, and 7 were classified into favorable-, intermediate-, and poor-risk groups, respectively, according to the Memorial Sloan-Kettering Cancer Center model, and 47 and 36 patients were administered mTORIs as second- and third-line therapy, respectively. As the best responses to mTORIs, 6, 53, and 24 were judged to have a partial response, stable disease, and progressive disease, respectively. The median progression-free survival (PFS) and overall survival (OS) of these patients following the introduction of mTORIs were 5.8 and 20.4 months, respectively. Of the several factors examined, liver metastasis and pretreatment C-reactive protein (CRP) level were shown to be independently associated with PFS, while only pretreatment CRP level had an independent impact on OS. Adverse events related to mTORIs corresponding to  $\geq$  grade 3 were observed in 26 patients, including anemia in 7, pneumonitis in 7, neutropenia in 4, and stomatitis in 3. Despite the low response rate, mTORIs are well tolerated and could provide comparatively favorable prognostic outcomes in Japanese patients with mRCC after the failure of TKIs.

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[281]

**TÍTULO / TITLE:** - A case of penile squamous cell carcinoma treated with a combination of antiepidermal growth factor receptor antibody and chemotherapy.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2014 Jan;25(1):123-5. doi: 10.1097/CAD.0000000000000024.

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

[1097/CAD.0000000000000024](#)

**AUTORES / AUTHORS:** - Men HT; Gou HF; Qiu M; He JP; Cheng K; Chen Y; Ge J; Liu JY

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Cancer Center, The State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, China.

**RESUMEN / SUMMARY:** - Our previous study showed that the features of epidermal growth factor receptor (EGFR)-RAS signaling in penile squamous cell carcinoma (SCC) suggested potential benefits of anti-EGFR monoclonal antibodies (mAbs) for penile SCC. Here, we report, for the first time, a combination of nimotuzumab (an EGFR mAb) with chemotherapy that resulted in a partial response in a 44-year-old patient with penile SCC, who developed bilateral inguinal node metastasis after primary partial penile amputation. The literature of case reports of anti-EGFR mAbs in penile SCC was also reviewed.

[282]

**TÍTULO / TITLE:** - Preoperative plasma fibrinogen predicts cervical metastasis in patients with stage I/II carcinoma of the tongue.

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

**REVISTA / JOURNAL:** - Int J Oral Maxillofac Surg. 2013 Oct 31. pii: S0901-5027(13)01097-7. doi: 10.1016/j.ijom.2013.09.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.ijom.2013.09.011](#)

**AUTORES / AUTHORS:** - Peng P; Shen J; Dong JB; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - School of Stomatology, China Medical University, Shenyang, People's Republic of China; Department of Oral and Maxillofacial Surgery, Tianjin Stomatological Hospital, Tianjin, People's Republic of China.

**RESUMEN / SUMMARY:** - The aim of this study was to evaluate the association of preoperative plasma fibrinogen levels with clinico-pathological parameters and disease-free survival in patients with oral tongue squamous cell carcinoma (OTSCC). We retrospectively studied 76 patients with OTSCC who underwent a partial glossectomy only, at a single centre, between 1996 and 2007. Among the 76 patients, 30 eventually developed cervical metastasis. Preoperative plasma fibrinogen levels were determined and correlated with clinico-pathological findings by t-test or analysis of variance methods. Univariate and multivariate analyses were used to determine the association of preoperative plasma fibrinogen levels and disease-free survival. Elevated levels of plasma fibrinogen were positively related with growth type ( $P < 0.001$ ), differentiation ( $P < 0.001$ ), thickness ( $P < 0.001$ ), and the infiltrative growth ratio ( $P = 0.032$ ). Univariate analysis showed that growth type ( $P < 0.001$ ), differentiation ( $P < 0.001$ ), thickness ( $P < 0.001$ ), and preoperative plasma fibrinogen levels ( $P < 0.001$ ) were significantly correlated with disease-free survival. Multivariate analysis showed

that the plasma fibrinogen level remained an independent factor for disease-free survival after partial glossectomy for OTSCC (P=0.029). A high preoperative plasma fibrinogen level is an independent predictor of cervical metastasis after partial glossectomy for OTSCC. A conservative supraomohyoid neck dissection is appropriate in patients with stage I/II carcinoma of the tongue whose preoperative plasma fibrinogen is >300mg/dl.

[283]

**TÍTULO / TITLE:** - Serum creatinine and creatinine clearance for predicting plasma methotrexate concentrations after high-dose methotrexate chemotherapy for the treatment for childhood lymphoblastic malignancies.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Oct 25.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2319-2](#)

**AUTORES / AUTHORS:** - Xu WQ; Zhang LY; Chen XY; Pan BH; Mao JQ; Song H; Li JY; Tang YM

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology-Oncology, Children's Hospital of Zhejiang University, School of Medicine, #57 Zhuganxiang Road, Yan-an Street, Hangzhou, 310003, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: Monitoring of plasma methotrexate (MTX) concentrations allows for therapeutic adjustments in treating childhood acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma (NHL) with high-dose MTX (HDMTX). We tested the hypothesis that assessment of creatinine clearance (CrCl) and/or serum Cr may be a suitable means of monitoring plasma MTX concentrations. METHODS: All children in the study had ALL or NHL, were in complete remission, and received HDMTX (3 or 5 g/m<sup>2</sup>)+leucovorin. Plasma MTX concentrations were measured at 24, 48, and 96 h. CrCl was determined at 24 and 48 h. Correlations between 24- and 48-h plasma MTX concentrations and CrCl and serum Cr concentrations were determined. CrCl and serum Cr concentrations were compared over time between children who had delayed and non-delayed MTX elimination. RESULTS: A total of 105 children were included. There were significant negative correlations between CrCl at 24 and 48 h and plasma MTX concentrations at 24 (both p < 0.001) and 48 h (both p < 0.001). There were significant positive correlations between serum Cr concentrations at both 24 and 48 h and plasma MTX concentrations at 24 (both p < 0.001) and 48 h (both p < 0.001). There were 88 (30.2 %) instances of elimination delay. Children with elimination delay had significantly lower CrCl and higher Cr concentrations at 24 and 48 h compared with children without elimination delay (all p < 0.05). CONCLUSION: Our findings suggest that, with further refinement, assessment of renal function may be a useful means of monitoring plasma MTX concentrations during HDMTX for ALL and NHL.

[284]

**TÍTULO / TITLE:** - 6]-Shogaol inhibits growth and induces apoptosis of non-small cell lung cancer cells by directly regulating Akt1/2.

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

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt365](#)

**AUTORES / AUTHORS:** - Kim MO; Lee MH; Oi N; Kim SH; Bae KB; Huang Z; Kim DJ; Reddy K; Lee SY; Park SJ; Kim JY; Xie H; Kundu JK; Ryoo ZY; Bode AM; Surh YJ; Dong Z

**INSTITUCIÓN / INSTITUTION:** - The Hormel Institute, University of Minnesota, MN 55912, USA.

**RESUMEN / SUMMARY:** - Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide. Despite progress in developing chemotherapeutics for the treatment of NSCLC, primary and secondary resistance limits therapeutic success. NSCLC cells exhibit multiple mutations in the epidermal growth factor receptor (EGFR), which cause aberrant activation of diverse cell signaling pathways. Therefore, suppression of the inappropriate amplification of EGFR downstream signaling cascades is considered to be a rational therapeutic and preventive strategy for the management of NSCLC. Our initial molecular-target oriented virtual screening revealed that the ginger components, including [6]-shogaol, [6]-paradol and [6]-gingerol, appear to be potential candidates for the prevention and treatment of NSCLC. Among the compounds, [6]-shogaol showed the greatest inhibitory effects on the NSCLC cell proliferation and anchorage-independent growth. [6]-Shogaol induced cell cycle arrest (G1 or G2/M) and apoptosis. Furthermore, [6]-shogaol inhibited Akt kinase activity, a downstream mediator of EGFR signaling, by binding with an allosteric site of Akt. In NCI-H1650 lung cancer cells, [6]-shogaol reduced the constitutive phosphorylation of STAT3 and decreased the expression of cyclin D1/3, which are target proteins in the Akt signaling pathway. The induction of apoptosis in NCI-H1650 cells by [6]-shogaol corresponded with the cleavage of caspase-3 and caspase-7. Moreover, intraperitoneal administration of [6]-shogaol inhibited the growth of NCI-H1650 cells as tumor xenografts in nude mice. [6]-Shogaol suppressed the expression of Ki-67, cyclin D1 and phosphorylated Akt and STAT3, and increased TUNEL-positivity in xenograft tumors. The present study clearly indicates that [6]-shogaol can be exploited for the prevention and/or treatment of NSCLC.

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[285]

**TÍTULO / TITLE:** - Ginsenoside F induces apoptosis in human gastric carcinoma cells through reactive oxygen species-mitochondria pathway and modulation of ASK-1/JNK signaling cascade in vitro and in vivo.

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

**REVISTA / JOURNAL:** - Phytomedicine. 2013 Nov 16. pii: S0944-7113(13)00422-4. doi: 10.1016/j.phymed.2013.10.013.

●● Enlace al texto completo (gratis o de pago) [1016/j.phymed.2013.10.013](#)

**AUTORES / AUTHORS:** - Mao Q; Zhang PH; Wang Q; Li SL

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Analysis & Metabolomics, Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, PR China.

**RESUMEN / SUMMARY:** - Ginsenoside F2 (F2) is a potential bioactive metabolite of major ginsenosides. The potential anti-cancer effect of F2 in gastric cancer cells has not been appraised. This study investigated the effects of F2 on the production of reactive oxygen species (ROS). We also investigated the in vitro and in vivo effects of F2 on the downstream signaling pathways leading to apoptosis in human gastric

cancer cells. The in vitro data revealed that F2 induces ROS accumulation followed by a decrease in mitochondrial transmembrane potential (MTP), and the release of cytochrome c (cyto c), which induced the caspase-dependent apoptosis. Further assay indicated that modulation of ASK-1/JNK pathway contributes to apoptosis. In vivo, F2 exhibits the obvious anti-cancer effect compared with cisplatin with no obvious toxicity. Jointly, these results suggest that F2 induces apoptosis by causing an accumulation of ROS and activating the ASK-1/JNK signaling pathway. This provides further support for the use of F2 as a novel anticancer therapeutic candidate.

[286]

**TÍTULO / TITLE:** - The combination of the serum carbohydrate antigen 19-9 and carcinoembryonic antigen is a simple and accurate predictor of mortality in pancreatic cancer patients.

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

**REVISTA / JOURNAL:** - Surg Today. 2013 Oct 9.

●● Enlace al texto completo (gratis o de pago) [1007/s00595-013-0752-9](#)

**AUTORES / AUTHORS:** - Kanda M; Fujii T; Takami H; Suenaga M; Inokawa Y; Yamada S; Nakayama G; Sugimoto H; Koike M; Nomoto S; Koderu Y

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan.

**RESUMEN / SUMMARY:** - PURPOSE: The aim of this study was to detect high-performance prognostic biomarkers of pancreatic cancer which would enable the identification of high-risk patients. METHODS: The subjects were 324 patients who underwent radical surgery for pancreatic ductal adenocarcinoma without neoadjuvant therapy. We evaluated the prognostic impact of four perioperative serum tumor markers, including carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA). We also evaluated the indices by multiplying the values of two tumor markers (e.g., CA19-9 x CEA). RESULTS: The preoperative CA19-9 x CEA index had a strong correlation with the prognosis of patients with pancreatic cancer, even when the cut-off was set at the median value. CA19-9 x CEA  $\geq 500$  was an independent predictor of mortality (hazard ratio: 1.642,  $p = 0.021$ ). In the ROC curve analysis of early mortality after surgery, the CA19-9 x CEA index had the highest goodness of fit. The presence of CA19-9 x CEA  $\geq 500$  had the largest attributable risk proportion because of its combined high predictive performance and prevalence. The postoperative CA19-9 x CEA index was also a significant predictive marker of mortality. CONCLUSION: The CA19-9 x CEA index is a strong prognostic biomarker that could help identify pancreatic cancer patients expected to have a poor prognosis so that they can be administered appropriate multidisciplinary treatment.

[287]

**TÍTULO / TITLE:** - Pheophorbide a-mediated photodynamic therapy induces autophagy and apoptosis via the activation of MAPKs in human skin cancer cells.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):137-44. doi: 10.3892/or.2013.2856. Epub 2013 Nov 19.

- Enlace al texto completo (gratis o de pago) [3892/or.2013.2856](#)

**AUTORES / AUTHORS:** - Yoon HE; Oh SH; Kim SA; Yoon JH; Ahn SG

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, College of Dentistry, Chosun University, Gwangju 501-759, Republic of Korea.

**RESUMEN / SUMMARY:** - Pheophorbide a (Pa), a chlorophyll derivative, is a photosensitizer that can induce significant antitumor effects in several types of tumor cells. The present study investigated the mechanism of Pa-mediated photodynamic therapy (Pa-PDT) in the human skin cancer cell lines A431 and G361. PDT significantly inhibited the cell growth in a Pa-concentration-dependent manner. We observed increased expression of Beclin-1, LC3B and ATG5, which are markers of autophagy, after PDT treatment in A431 cells but not in G361 cells. In G361 cells, Pa-PDT strongly induced PARP cleavage and subsequent apoptosis, which was confirmed using Annexin V/Propidium iodide double staining. Pa-PDT predominantly exhibited its antitumor effects via activation of ERK1/2 and p38 in A431 and G361 cells, respectively. An in vivo study using the CAM xenograft model demonstrated that Pa-PDT strongly induced autophagy and apoptosis in A431-transplanted tumors and/or apoptosis in G361-transplanted tumors. These results may provide a basis for understanding the underlying mechanisms of Pa-PDT and for developing Pa-PDT as a therapy for skin cancer.

[288]

**TÍTULO / TITLE:** - Extra virgin olive oil potentiates the effects of aromatase inhibitors via glutathione depletion in estrogen receptor-positive human breast cancer (MCF-7) cells.

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

**REVISTA / JOURNAL:** - Food Chem Toxicol. 2013 Dec;62:817-24. doi: 10.1016/j.fct.2013.10.024. Epub 2013 Oct 23.

- Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.10.024](#)

**AUTORES / AUTHORS:** - Ismail AM; In LL; Tasyriq M; Syamsir DR; Awang K; Omer Mustafa AH; Idris OF; Fadl-Elmula I; Hasima N

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Faculty of Medicine and Health Sciences, Al-Neelain University, 12702 Khartoum, Sudan; Department of Biochemistry, Faculty of Science and Technology, Al-Neelain University, 12702 Khartoum, Sudan. Electronic address: [amargggu@yahoo.com](mailto:amargggu@yahoo.com).

**RESUMEN / SUMMARY:** - There have been numerous evidences supporting the relationship between olive oil and cancer, with most of the attention being directed toward its fat and phenolic content. The aims of this study were to investigate whether EVOO and OA could enhance the effects of aromatase inhibitors (letrozole and anastrozole) in ER-positive MCF-7 cells, as well as to investigate its influence on cytochrome c release and GSH levels. It was observed that upon combination treatment, anti-proliferation effects and apoptosis induction were augmented. Apoptosis was triggered via the intrinsic pathway in accordance with cytochrome c release into the cytosol based on IF-IC and ELISA observations. Intracellular GSH levels were also reduced upon EVOO/OA treatment in combination with aromatase inhibitors, and were found to be inversely correlated to cytosolic cytochrome c levels. Additionally, the estrogenic suppressive effects of letrozole and anastrozole were amplified when used in combination with EVOO/OA. Therefore, the employment of aromatase inhibitors in

combination with EVOO/OA could orchestrate a reduction in intracellular estrone biosynthesis which feeds ER-positive cells, while simultaneously depleting GSH levels and increasing ROS generation, thus releasing cytochrome c and subsequent induction of apoptosis in MCF-7 cells.

[289]

**TÍTULO / TITLE:** - Successful Treatment of Metastasized Pancreatic Vasoactive Intestinal Polypeptide-Secreting Tumor Unresponsive to High-Dose Octreotide by Peptide Receptor Radionuclide Therapy Using 90Y DOTATATE.

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

**REVISTA / JOURNAL:** - Clin Nucl Med. 2013 Dec;38(12):996-7. doi: 10.1097/RLU.0b013e3182a7596b.

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

[1097/RLU.0b013e3182a7596b](#)

**AUTORES / AUTHORS:** - Sainz-Esteban A; Baum RP

**INSTITUCIÓN / INSTITUTION:** - From the \*Department of Nuclear Medicine, Hospital Clínico Universitario de Valladolid, Valladolid, España; and daggerTHERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging, ENETS Center of Excellence, Zentralklinik Bad Berka, Bad Berka, Germany.

**RESUMEN / SUMMARY:** - We report a successful treatment of a patient with heavily metastasized pancreatic vasoactive intestinal polypeptide-secreting tumor, which was unresponsive to high doses of octreotide analog using peptide receptor radionuclide therapy applying a radiolabeled somatostatin analog. After the peptide receptor radionuclide therapy, there was a decrease in vasoactive intestinal polypeptide levels, a significant reduction in somatostatin receptor expression and in molecular tumor volume on Ga DOTANOC PET/CT scan, and a complete long-term resolution of symptoms of the patient.

[290]

**TÍTULO / TITLE:** - Purvalanol A is a strong apoptotic inducer via activating polyamine catabolic pathway in MCF-7 estrogen receptor positive breast cancer cells.

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

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1007/s11033-013-2847-1](#)

**AUTORES / AUTHORS:** - Obakan P; Arisan ED; Ozfiliz P; Coker-Gurkan A; Palavan-Unsal N

**INSTITUCIÓN / INSTITUTION:** - Molecular Biology and Genetics Department, Science and Literature Faculty, Istanbul Kultur University, Atakoy Campus, 34156, Istanbul, Turkey.

**RESUMEN / SUMMARY:** - Purvalanol A is a specific CDK inhibitor which triggers apoptosis by causing cell cycle arrest in cancer cells. Although it has strong apoptotic potential, the mechanistic action of Purvalanol A on significant cell signaling targets has not been clarified yet. Polyamines are crucial metabolic regulators affected by CDK inhibition because of their role in cell cycle progress as well. In addition, malignant cells possess impaired polyamine homeostasis with high level of intracellular polyamines. Especially induction of polyamine catabolic enzymes spermidine/spermine N1-

acetyltransferase (SSAT), polyamine oxidase (PAO) and spermine oxidase (SMO) induced toxic by-products in correlation with the induction of apoptosis in cancer cells. In this study, we showed that Purvalanol A induced apoptosis in caspase- dependent manner in MCF-7 ER(+) cells, while MDA-MB-231 (ER-) cells were less sensitive against drug. In addition Bcl-2 is a critical target for Purvalanol A, since Bcl-2 overexpressed cells are more resistant to Purvalanol A-mediated apoptosis. Furthermore, exposure of MCF-7 cells to Purvalanol A triggered SSAT and PAO upregulation and the presence of PAO/SMO inhibitor, MDL 72,527 prevented Purvalanol A-induced apoptosis.

[291]

**TÍTULO / TITLE:** - Radio-sensitization of human leukaemic MOLT-4 cells by DNA-dependent protein kinase inhibitor, NU7441.

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

**REVISTA / JOURNAL:** - Radiat Environ Biophys. 2013 Oct 8.

•• Enlace al texto completo (gratis o de pago) [1007/s00411-013-0494-5](#)

**AUTORES / AUTHORS:** - Tichy A; Durisova K; Salovska B; Pejchal J; Zarybnicka L; Vavrova J; Dye NA; Sinkorova Z

**INSTITUCIÓN / INSTITUTION:** - Department of Radiobiology, Faculty of Health Sciences in Hradec Kralove, University of Defence in Brno, Brno, Czech Republic, [tichy@pmfhk.cz](mailto:tichy@pmfhk.cz).

**RESUMEN / SUMMARY:** - We studied the effect of pre-incubation with NU7441, a specific inhibitor of DNA-dependent protein kinase (DNA-PK), on molecular mechanisms triggered by ionizing radiation (IR). The experimental design involved four groups of human T-lymphocyte leukaemic MOLT-4 cells: control, NU7441-treated (1 µM), IR-treated (1 Gy), and combination of NU7441 and IR. We used flow cytometry for apoptosis assessment, Western blotting and ELISA for detection of proteins involved in DNA repair signalling and epifluorescence microscopy for detection of IR-induced phosphorylation of histone H2A.X. We did not observe any major changes in the amount of DNA-PK subunits Ku70/80 caused by the combination of NU7441 and radiation. Their combination led to an increased phosphorylation of H2A.X, a hallmark of DNA damage. However, it did not prevent up-regulation of neither p53 (and its phosphorylation at Ser 15 and 392) nor p21. We observed a decrease in the levels of anti-apoptotic Mcl-1, cdc25A phosphatase, cleavage of PARP and a significant increase in apoptosis in the group treated with combination. In conclusion, the combination of NU7441 with IR caused increased phosphorylation of H2A.X early after irradiation and subsequent induction of apoptosis. It was efficient in MOLT-4 cells in 10x lower concentration than the inhibitor NU7026. NU7441 proved as a potent radio-sensitizing agent, and it might provide a platform for development of new radio-sensitizers in radiotherapy.

[292]

**TÍTULO / TITLE:** - In vivo analysis of insulin-like growth factor type 1 receptor humanized monoclonal antibody MK-0646 and small molecule kinase inhibitor OSI-906 in colorectal cancer.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):87-94. doi: 10.3892/or.2013.2819. Epub 2013 Oct 25.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2819](https://doi.org/10.3892/or.2013.2819)

**AUTORES / AUTHORS:** - Leiphrakpam PD; Agarwal E; Mathiesen M; Haferbier KL; Brattain MG; Chowdhury S

**INSTITUCIÓN / INSTITUTION:** - Eppley Cancer Center, University of Nebraska Medical Center, Omaha, NE 68198-5950, USA.

**RESUMEN / SUMMARY:** - The development and characterization of effective anticancer drugs against colorectal cancer (CRC) is of urgent need since it is the second most common cause of cancer death. The study was designed to evaluate the effects of two IGF-1R antagonists, MK-0646, a recombinant fully humanized monoclonal antibody and OSI-906, a small molecule tyrosine kinase inhibitor on CRC cells. Xenograft study was performed on IGF-1R-dependent CRC cell lines for analyzing the antitumor activity of MK-0646 and OSI-906. Tumor proliferation and apoptosis were assessed using Ki67 and TUNEL assays, respectively. We also performed in vitro characterization of MK-0646 and OSI-906 treatment on CRC cells to identify mechanisms associated with drug-induced cell death. Exposure of the GEO and CBS tumor xenografts to MK-0646 or OSI-906 led to a decrease in tumor growth. TUNEL analysis showed an increase of approximately 45-55% in apoptotic cells in both MK-0646 and OSI-906 treated tumor samples. We report the novel finding that treatment with IGF-1R antagonists led to downregulation of X-linked inhibitor of apoptosis (XIAP) protein involved in cell survival and inhibition of cell death. In conclusion, IGF-1R antagonists (MK-0646 and OSI-906) demonstrated single agent inhibition of subcutaneous CRC xenograft growth. This was coupled to pro-apoptotic effects resulting in downregulation of XIAP and inhibition of cell survival. We report a novel mechanism by which MK-0646 and OSI-906 elicits cell death in vivo and in vitro. Moreover, these results indicate that MK-0646 and OSI-906 may be potential anticancer candidates for the treatment of patients with IGF-1R-dependent CRC.

[293]

**TÍTULO / TITLE:** - Antitumoral activity of lenalidomide in in vitro and in vivo models of mantle cell lymphoma involves the destabilization of cyclin D1/p27KIP1 complexes.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1569](https://doi.org/10.1158/1078-0432.CCR-13-1569)

**AUTORES / AUTHORS:** - Moros A; Bustany S; Cahu J; Saborit-Villarroya I; Martinez A; Colomer D; Sola B; Roue G

**INSTITUCIÓN / INSTITUTION:** - Hemato-oncology, IDIBAPS.

**RESUMEN / SUMMARY:** - PURPOSE: Clinical responses to the immunomodulatory drug lenalidomide have been observed in patients with relapsed/refractory mantle cell lymphoma (MCL), although its mechanism of action remains partially unknown. We investigated whether the expression and subcellular localization of cyclin D1, a major cell cycle regulator overexpressed in MCL, and the cyclin-dependent kinase inhibitor p27KIP1, could identify MCL cases sensitive to lenalidomide, and whether the compound could modulate cyclin D1/p27KIP1 complexes in MCL cells.

EXPERIMENTAL DESIGN: MCL primary samples and cell lines were analyzed for sub-

cellular levels of cyclin D1/p27KIP1 complexes by Western blot, immunohistochemistry, immunoprecipitation and flow cytometry. Activity of lenalidomide in vitro and its effect on cyclin D1/p27KIP1 complexes were evaluated by RT-PCR, immunoprecipitation, immunofluorescence and Western blot. In vivo validation was carried out in a mouse xenograft model of human MCL. RESULTS: We found cyclin D1 and p27KIP1 to be coordinately expressed in all the MCL samples tested. Immunoprecipitation analyses and siRNA assays suggested a direct role of cyclin D1 in the regulation of p27KIP1 levels. The nuclear accumulation of both proteins correlated with MCL cell tumorigenicity in vivo, and sensitivity to lenalidomide activity in vitro and in vivo. Lenalidomide mechanism of action relied on cyclin D1 downregulation and disruption of cyclin D1/p27KIP1 complexes, followed by cytosolic accumulation of p27KIP1, cell proliferation arrest, apoptosis, and angiogenesis inhibition. CONCLUSIONS: These results highlight a mechanism of action of lenalidomide in MCL cases with increased tumorigenicity in vivo, which is mediated by the dissociation of cyclin D1/p27KIP1 complexes, and subsequent proliferation blockade and apoptosis induction.

[294]

**TÍTULO / TITLE:** - Halofuginone induces the apoptosis of breast cancer cells and inhibits migration via downregulation of matrix metalloproteinase-9.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):309-18. doi: 10.3892/ijo.2013.2157. Epub 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2157](#)

**AUTORES / AUTHORS:** - Jin ML; Park SY; Kim YH; Park G; Lee SJ

**INSTITUCIÓN / INSTITUTION:** - Department of Microbiology, Pusan National University, Busan 609-735, Republic of Korea.

**RESUMEN / SUMMARY:** - Halofuginone (HF) is extracted from *Dichroa febrifuga*, a plant used in traditional medicine. We report that the HF extract inhibits the growth of breast cancer cells and induces the generation of reactive oxygen species (ROS) and apoptosis, an important feature of potential anticancer agents. In addition, HF significantly reduces the migration and invasion of MCF-7 and MDA-MB-231 human breast cancer cells after 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulation. As matrix metalloproteinase-9 plays a critical role in tumor metastasis, we analyzed its expression with the HF extract treatment. Western blot analysis and gelatin zymography showed that HF suppresses MMP-9 expression and activity concentration-dependently. HF also decreases the nuclear protein levels of nuclear factor kappa B (NF-kappaB) and c-fos (AP-1), critical transcription factors regulating MMP-9 expression through binding the MMP-9 promoter region. Luciferase assays showed that HF decreases TPA-induced MMP-9 promoter binding activities of NF-kappaB and AP-1. Taken together, these are the first results indicating that halofuginone may represent a promising new agent for breast cancer chemotherapy.

[295]

**TÍTULO / TITLE:** - Prognostic significance of let-7b expression in breast cancer and correlation to its target gene of BSG expression.

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

**REVISTA / JOURNAL:** - Med Oncol. 2014 Jan;31(1):773. doi: 10.1007/s12032-013-0773-7. Epub 2013 Nov 22.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0773-7](#)

**AUTORES / AUTHORS:** - Ma L; Li GZ; Wu ZS; Meng G

**INSTITUCIÓN / INSTITUTION:** - Department of Pathophysiology, Bengbu Medical College, Bengbu, 233030, China.

**RESUMEN / SUMMARY:** - Let-7 microRNAs (miRNAs) are found in a wide range of species, and alterations of let-7 miRNA family member expression levels in humans are associated with various types of cancer. However, few researchers have reported alterations in let-7b levels in breast cancer (BC). Specifically, the use of altered let-7 expression as a prognostic biomarker is of particular interest and significance. The aim of this study was to investigate whether let-7b could be used as a biomarker of tumor progression and patient prognosis in BC and to determine the target gene of let-7b. We retrospectively analyzed the clinical pathological characteristics of 80 BC. We utilized digoxigenin-labeled locked nucleic acid-miRNA probes to detect let-7b expression in 80 BC and 22 benign breast disease (BBD) histologic specimens by in situ hybridization, and also detect the expression of BSG-a potential target gene of let-7b-by immunohistochemistry. We observed that the levels of let-7b expression in BBD were higher than in BC specimens ( $P < 0.05$ ), indicating that let-7b could inhibit growth and facilitate differentiation of BBD. Also, loss of let-7b expression on BC tissue specimens raised the possibility that let-7b could play a crucial role in the pathogenesis of BC. Furthermore, let-7b expression in breast cancer patients was inversely associated with tumor lymph node metastasis ( $P = 0.001$ ), patient overall survival ( $P = 0.027$ ), relapse-free survival ( $P = 0.016$ ), and BSG protein expression ( $P = 0.001$ ). Breast cancer patients with low let-7b expression had poor prognoses, indicating let-7b might act as cancer suppressor gene in BC development and progression by inhibiting the expression of BSG.

[296]

**TÍTULO / TITLE:** - A revised NOTCH1 mutation frequency still impacts survival while the allele burden predicts early progression in chronic lymphocytic leukemia.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Oct 9. doi: 10.1038/leu.2013.289.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.289](#)

**AUTORES / AUTHORS:** - Sportoletti P; Baldoni S; Del Papa B; Aureli P; Dorillo E; Ruggeri L; Plebani S; Amico V; Di Tommaso A; Rosati E; Marconi P; Di Ianni M; Falzetti F

**INSTITUCIÓN / INSTITUTION:** - Hematology and Clinical Immunology Section, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy.

[297]

**TÍTULO / TITLE:** - Cytoskeleton-associated protein 2 is a potential predictive marker for risk of early and extensive recurrence of hepatocellular carcinoma after operative resection.

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

**REVISTA / JOURNAL:** - Surgery. 2013 Nov 12. pii: S0039-6060(13)00331-0. doi: 10.1016/j.surg.2013.06.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.surg.2013.06.009](http://1016/j.surg.2013.06.009)

**AUTORES / AUTHORS:** - Hayashi T; Ohtsuka M; Okamura D; Seki N; Kimura F; Shimizu H; Yoshidome H; Kato A; Yoshitomi H; Furukawa K; Miyazaki M

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: De principio transplantation is an attractive strategy for the treatment of patients with hepatocellular carcinoma (HCC). The most important issue for this strategy is how to predict the risk of early and extensive recurrence. The present study aimed to identify a molecule associated with early and extensive recurrence of HCC after resection. METHODS: Differentially expressed genes were screened by DNA microarray analysis with the use of 12 HCC samples from patients who had different clinical courses based on the timing and extent of recurrence after operative resection. Furthermore, the obtained results were validated in 60 independent samples by quantitative real-time reverse transcription-polymerase chain reaction. Immunohistochemistry was performed to assess gene expression at the protein level. RESULTS: Microarray analysis and quantitative reverse transcription-polymerase chain reaction revealed cytoskeleton-associated protein 2 (CKAP2) as a candidate gene associated with early and extensive recurrence of HCC after resection. This observation was confirmed through examination of independent set samples, in which patients with greater-level CKAP2 mRNA expression exhibited shorter recurrence-free survival. Immunohistochemistry showed CKAP2 protein expression was associated with early ( $\leq 3$  years) and extensive recurrence (beyond Milan criteria) after operative resection. CONCLUSION: Immunohistochemical CKAP2 expression might be a potential biologic marker for identifying HCC patients at risk of early and extensive recurrence after operative resection.

[298]

**TÍTULO / TITLE:** - A Gene Signature Combining the Tissue Expression of Three Angiogenic Factors is a Prognostic Marker in Early-stage Non-small Cell Lung Cancer.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Oct 22.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3330-x](http://1245/s10434-013-3330-x)

**AUTORES / AUTHORS:** - Sanmartin E; Sirera R; Uso M; Blasco A; Gallach S; Figueroa S; Martinez N; Hernando C; Honguero A; Martorell M; Guijarro R; Rosell R; Jantus-Lewintre E; Camps C

**INSTITUCIÓN / INSTITUTION:** - Molecular Oncology Laboratory, Fundacion Investigacion, Hospital General Universitario de Valencia, Valencia, España.

**RESUMEN / SUMMARY:** - BACKGROUND: Angiogenesis and lymphangiogenesis are key mechanisms for tumor growth and dissemination. They are mainly regulated by the vascular endothelial growth factor (VEGF) family of ligands and receptors. The aim of this study was to analyze relative expression levels of angiogenic markers in resectable non-small cell lung cancer patients in order to assess a prognostic signature that could improve characterization of patients with worse clinical outcomes. METHODS: RNA was obtained from tumor and normal lung specimens from 175 patients. Quantitative polymerase chain reaction was performed to analyze the relative expression of HIF1A,

PIGF, VEGFA, VEGFA165b, VEGFB, VEGFC, VEGFD, VEGFR1, VEGFR2, VEGFR3, NRP1 and NRP2. RESULTS: Univariate analysis showed that tumor size and ECOG-PS are prognostic factors for time to progression (TTP) and overall survival (OS). This analysis in the case of angiogenic factors also revealed that PIGF, VEGFA, VEGFB and VEGFD distinguish patients with different outcomes. Taking into account the complex interplay between the different ligands of the VEGF family and to more precisely predict the outcome of the patients, we considered a new analysis combining several VEGF ligands. In order to find independent prognostic variables, we performed a multivariate Cox analysis, which showed that the subgroup of patients with higher relative expression of VEGFA plus lower VEGFB and VEGFD presented the poorest outcome for both TTP and OS. CONCLUSIONS: The relative expression of these three genes can be considered as an angiogenic gene signature whose applicability for the selection of candidates for targeted therapies needs to be further validated.

[299]

**TÍTULO / TITLE:** - The induction of apoptosis by a newly synthesized diosgenyl saponin through the suppression of estrogen receptor-alpha in MCF-7 human breast cancer cells.

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

**REVISTA / JOURNAL:** - Arch Pharm Res. 2013 Nov 22.

●● Enlace al texto completo (gratis o de pago) [1007/s12272-013-0279-z](#)

**AUTORES / AUTHORS:** - Chun J; Han L; Xu MY; Wang B; Cheng MS; Kim YS

**INSTITUCIÓN / INSTITUTION:** - Natural Products Research Institute, College of Pharmacy, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul, 151-742, Republic of Korea.

**RESUMEN / SUMMARY:** - Estrogen receptor (ER)-alpha is an important therapeutic target in the clinical treatment of breast cancer. A potential down-regulator of ER-alpha, diosgenyl alpha-L-rhamnopyranosyl-(1-->2)-[beta-D-xylopyranosyl-(1-->4)]-alpha-L-arabinopyranoside is a newly synthesized diosgenyl saponin named compound 22. This study evaluated the in vitro mechanism of compound 22 as an anticancer agent for breast cancer. Our results indicated that compound 22 selectively inhibited proliferation and induced apoptosis in ER-positive MCF-7 cells, compared with ER-negative MDA-MB-231 and MCF-10A cells. Western blot analysis showed that compound 22 decreased the expression of procaspase-3, procaspase-8, and survivin; and increased the expression of Fas ligand and cleaved PARP1 in MCF-7 cells, indicating that compound 22-induced apoptosis was mediated by the extrinsic pathway. This apoptosis was associated with the suppression of ER-alpha protein and mRNA expression and the inhibition of ER-DNA binding to the estrogen responsive element. Moreover, ER-alpha mediated gene expression such as c-Myc and cyclin D1 was reduced, and the activation of p38 and ERK 1/2 was significantly decreased after treatment with compound 22 in MCF-7 cells. Taken together, these results demonstrate that compound 22 down-regulates ER-alpha expression and induces apoptosis through the extrinsic pathway, suggesting that compound 22 may be effective in the treatment of ER-positive breast cancer.

[300]

**TÍTULO / TITLE:** - The Residual Tumor Autophagy Marker LC3B Serves as a Prognostic Marker in Local Advanced Breast Cancer after Neoadjuvant Chemotherapy.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1617](#)

**AUTORES / AUTHORS:** - Chen S; Jiang YZ; Huang L; Zhou RJ; Yu KD; Liu Y; Shao ZM

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Breast Surgery, and Pathology, Fudan University Shanghai Cancer Center/Cancer Institute; Department of Oncology, Shanghai Medical College; and Institutes of Biomedical Science, Fudan University, Shanghai, PR China.

**RESUMEN / SUMMARY:** - PURPOSE: This study sought to investigate the prognostic value of the autophagy marker microtubule-associated protein chain 3B (LC3B) in patients with residual tumors after neoadjuvant chemotherapy (NCT) for locally advanced breast cancer (LABC). Patients and Methods: The expression of LC3B in residual breast cancer cells was assessed by immunohistochemistry in surgical specimens from 229 patients diagnosed with histologically proven invasive breast cancer. All patients underwent NCT followed by mastectomy and were considered nonpathologic complete responders (non-pCR) after a pathologic evaluation. The prognostic value of various clinicopathologic factors was evaluated. RESULTS: The LC3B density was similar between the peripheral and central area of the tumors ( $P = 0.328$ ) but was significantly lower in the extratumoral area ( $P < 0.001$  and  $P < 0.001$ , respectively). Furthermore, LC3B density, which correlated with Beclin-1 expression, Ki-67 index, and breast cancer subtype, served as an independent prognostic factor for both relapse-free survival (RFS;  $P = 0.012$ ) and overall survival (OS;  $P = 0.008$ ); the prognostic value of LC3B was most significant in triple-negative patients. Using a combination of LC3B expression and the status of residual involved lymph nodes, the patients were classified into four groups with different risks of relapse and death ( $P < 0.001$  for RFS and  $P = 0.003$  for OS). CONCLUSION: LC3B can be used as a prognostic marker in patients with non-pCR after NCT for breast cancer, which highlights the importance of autophagy in the biologic behavior of chemoresistant cancer cells. Furthermore, evaluating and targeting autophagy in the neoadjuvant setting may help prevent disease relapse in patients with non-pCR. Clin Cancer Res; 1-10. ©2013 AACR.

[301]

**TÍTULO / TITLE:** - Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Oct;141(3):507-14. doi: 10.1007/s10549-013-2711-y. Epub 2013 Oct 9.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2711-y](#)

**AUTORES / AUTHORS:** - Lobbezoo DJ; van Kampen RJ; Voogd AC; Dercksen MW; van den Berkmoortel F; Smilde TJ; van de Wouw AJ; Peters FP; van Riel JM; Peters NA; de Boer M; Borm GF; Tjan-Heijnen VC

**INSTITUCIÓN / INSTITUTION:** - Maastricht University Medical Center, P.O. Box 5800, 6202 AZ, Maastricht, The Netherlands.

**RESUMEN / SUMMARY:** - Contrary to the situation in early breast cancer, little is known about the prognostic relevance of the hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) in metastatic breast cancer. The objectives of this study were to present survival estimates and to determine the prognostic impact of breast cancer subtypes based on HR and HER2 status in a recent cohort of metastatic breast cancer patients, which is representative of current clinical practice. Patients diagnosed with metastatic breast cancer between 2007 and 2009 were included. Information regarding patient and tumor characteristics and treatment was collected. Patients were categorized in four subtypes based on the HR and HER2 status of the primary tumor: HR positive (+)/HER2 negative (-), HR+/HER2+, HR-/HER2+ and triple negative (TN). Survival was estimated using the Kaplan-Meier method. Cox proportional hazards model was used to determine the prognostic impact of breast cancer subtype, adjusted for possible confounders. Median follow-up was 21.8 months for the 815 metastatic breast cancer patients included; 66 % of patients had the HR+/HER2- subtype, 8 % the HR-/HER2+ subtype, 15 % the TN subtype and 11 % the HR+/HER2+ subtype. The longest survival was observed for the HR+/HER2+ subtype (median 34.4 months), compared to 24.8 months for the HR+/HER2- subtype, 19.8 months for the HR-/HER2+ subtype and 8.8 months for the TN subtype (P < 0.0001). In the multivariate analysis, subtype was an independent prognostic factor, as were initial site of metastases and metastatic-free interval. The HR+/HER2+ subtype was associated with the longest survival after diagnosis of distant metastases.

[302]

**TÍTULO / TITLE:** - Dual Targeting of HER2-Positive Cancer with Trastuzumab Emtansine and Pertuzumab: Critical Role for Neuregulin Blockade in Antitumor Response to Combination Therapy.

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

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

- [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-0358](#)

**AUTORES / AUTHORS:** - Phillips GD; Fields CT; Li G; Dowbenko D; Schaefer G; Miller K; Andre F; Burris HA 3rd; Albain KS; Harbeck N; Dieras V; Crivellari D; Fang L; Guardino E; Olsen SR; Crocker LM; Sliwkowski MX

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Research Oncology, Departments of Biostatistics, Product Development Oncology, and Translational Oncology, Genentech, Inc., South San Francisco, California; Indiana University Simon Cancer Center, Indianapolis, Indiana; Institute Gustave Roussy, Villejuif; Department of Medical Oncology, Institut Curie, Paris, France; Sarah Cannon Research Institute, Nashville, Tennessee; Loyola University Medical Center, Maywood, Illinois; University of Munich, Munich, Germany; and Division of Medical Oncology, Centro di Riferimento Oncologico, Istituto Nazionale Tumori Aviano, Italy.

**RESUMEN / SUMMARY:** - PURPOSE: Targeting HER2 with multiple HER2-directed therapies represents a promising area of treatment for HER2-positive cancers. We investigated combining the HER2-directed antibody-drug conjugate trastuzumab emtansine (T-DM1) with the HER2 dimerization inhibitor pertuzumab (Perjeta). EXPERIMENTAL DESIGN: Drug combination studies with T-DM1 and pertuzumab were performed on cultured tumor cells and in mouse xenograft models of

HER2-amplified cancer. In patients with HER2-positive locally advanced or metastatic breast cancer (mBC), T-DM1 was dose-escalated with a fixed standard pertuzumab dose in a 3+3 phase Ib/II study design. RESULTS: Treatment of HER2-overexpressing tumor cells in vitro with T-DM1 plus pertuzumab resulted in synergistic inhibition of cell proliferation and induction of apoptotic cell death. The presence of the HER3 ligand, heregulin (NRG-1beta), reduced the cytotoxic activity of T-DM1 in a subset of breast cancer lines; this effect was reversed by the addition of pertuzumab. Results from mouse xenograft models showed enhanced antitumor efficacy with T-DM1 and pertuzumab resulting from the unique antitumor activities of each agent. In patients with mBC previously treated with trastuzumab, lapatinib, and chemotherapy, T-DM1 could be dosed at the maximum tolerated dose (MTD; 3.6 mg/kg every 3 weeks) with standard dose pertuzumab. Adverse events were mostly grade 1 and 2, with indications of clinical activity. CONCLUSIONS: Dual targeting of HER2 with the combination of T-DM1 and pertuzumab in cell culture and mouse xenograft models resulted in enhanced antitumor activity. In patients, this combination showed an encouraging safety and tolerability profile with preliminary evidence of efficacy. Clin Cancer Res; 20(2); 1-13. ©2013 AACR.

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[303]

**TÍTULO / TITLE:** - A novel ribonuclease with antiproliferative activity toward leukemia and lymphoma cells and HIV-1 reverse transcriptase inhibitory activity from the mushroom, *Hohenbuehelia serotina*.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2014 Jan;33(1):209-14. doi: 10.3892/ijmm.2013.1553. Epub 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1553](#)

**AUTORES / AUTHORS:** - Zhang R; Zhao L; Wang H; Ng TB

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory for Agrobiotechnology and Department of Microbiology, China Agricultural University, Beijing 100193, P.R. China.

**RESUMEN / SUMMARY:** - In this study, a 27-kDa ribonuclease (RNase) was purified from the dried fruiting bodies of the mushroom, *Hohenbuehelia serotina*. The isolation protocol involved anion exchange chromatography, affinity chromatography, cation exchange chromatography and gel filtration in succession. The RNase was unadsorbed on DEAE-cellulose, but was adsorbed on Affi-gel blue gel and CM-cellulose. The N-terminal amino acid sequence was TVGGSLAEKGN which showed homology to other fungal RNases to a certain degree. The RNase exhibited maximal RNase activity at pH 5 and 80 C. It demonstrated the highest ribonucleolytic activity toward poly(C), a relatively high activity toward poly(U), and a considerably weaker activity toward poly(A) and (G). The RNase inhibited human immunodeficiency virus type 1 (HIV-1) reverse transcriptase with an IC50 of 50 microM and reduced [3H-methyl]-thymidine uptake by L1210 leukemia cells and MBL2 lymphoma cells with an IC50 of 25 microM and 40 microM, respectively.

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[304]

**TÍTULO / TITLE:** - Poly (ADP-ribose) polymerase inhibitor LT-626: Sensitivity correlates with MRE11 mutations and synergizes with platinum and irinotecan in colorectal cancer cells.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Nov 9. pii: S0304-3835(13)00799-4. doi: 10.1016/j.canlet.2013.10.034.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.10.034](#)

**AUTORES / AUTHORS:** - McPherson LA; Shen Y; Ford JM

**INSTITUCIÓN / INSTITUTION:** - Division of Oncology, Stanford University School of Medicine, Stanford, CA, United States.

**RESUMEN / SUMMARY:** - Some colorectal cancers (CRC) display microsatellite instability (MSI) leading to mutations in genes such as MRE11. The aim of this study was to determine whether MSI or MRE11 mutational status correlates with sensitivity to the PARP inhibitor LT-626 and whether LT-626 synergizes with DNA-damaging chemotherapeutic agents. CRC cells harboring biallelic MRE11 mutations were more sensitive to LT-626 and stable overexpression or knock-down of MRE11 in cell lines correlated with sensitivity. Synergism was evident between LT-626 and cisplatin, oxaliplatin and SN-38 suggesting that PARP inhibitors in combination with DNA damaging agents may be a successful strategy for treatment of CRC.

[305]

**TÍTULO / TITLE:** - Reversal of multidrug resistance phenotype in human breast cancer cells using doxorubicin-liposome-microbubble complexes assisted by ultrasound.

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

**REVISTA / JOURNAL:** - J Control Release. 2013 Nov 25. pii: S0168-3659(13)00919-X. doi: 10.1016/j.jconrel.2013.11.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.jconrel.2013.11.018](#)

**AUTORES / AUTHORS:** - Deng Z; Yan F; Jin Q; Li F; Wu J; Liu X; Zheng H

**INSTITUCIÓN / INSTITUTION:** - Paul C. Lauterbur Research Center for Biomedical Imaging, Institute of Biomedical and Health Engineering, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China.

**RESUMEN / SUMMARY:** - The circumvention of multidrug resistance (MDR) plays a critically important role in the success of chemotherapy. The aim of this work is to investigate the effectiveness and possible mechanisms of the reversal of MDR phenotype in human breast cancer cells by using doxorubicin-liposome-microbubble complexes (DLMC) assisted by ultrasound (US). DLMC is fabricated through conjugating doxorubicin (DOX)-liposome (DL) to the surface of microbubbles (MBs) via the biotin-avidin linkage. The resulting drug-loaded complexes are then characterized and incubated with MCF-7/ADR human breast cancer cells and followed by US exposure. Our results show the more rapid cellular uptake, evident enhancement of nuclear accumulation and less drug efflux in the resistant cells treated by DLMC+US than those treated by DL, DL+verapamil under the same US treatment or DLMC without US. The enhanced drug delivery and cellular uptake also associated with the increase of cytotoxicity against MCF-7/ADR cells, lower MCF-7/ADR cell viability and higher apoptotic cells. Mechanism investigations further disclose a significant increase of reactive oxygen species (ROS) level, enhanced DNA damage and obvious reduction of P-glycoprotein expression in the resistant cells treated with DLMC+US compared

with the control cases of cells treated by DLMC, DL+US or DL+verapamil+US. In conclusion, our study demonstrates that DLMC in combination with US may provide an effective delivery of drug to sensitize cells to circumvent MDR and to enhance the therapeutic index of the chemotherapy.

[306]

**TÍTULO / TITLE:** - Breast Cancer Biomarkers: Risk Assessment, Diagnosis, Prognosis, Prediction of Treatment Efficacy and Toxicity, and Recurrence.

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

**REVISTA / JOURNAL:** - Curr Pharm Des. 2013 Nov 25.

**AUTORES / AUTHORS:** - M Braden A; V Stankowski R; M Engel J; A Onitilo A

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology/Oncology, Marshfield Clinic Weston Center, 3501 Cranberry Boulevard, Weston, WI 54476 USA.

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**RESUMEN / SUMMARY:** - Breast cancer is the most common cancer amongst women in the United States and around the world. Although widespread use of adjuvant chemotherapeutic and hormonal agents has improved mortality from breast cancer, it remains challenging to determine on an individual basis who will benefit from such treatments and who will be likely to encounter toxicities. With the rising costs of healthcare and the introduction of new targeted therapies, use of biomarkers has emerged as a method of assisting with breast cancer diagnosis, prognosis, prediction of therapeutic response, and surveillance of disease during and after treatment. In the following review, prognostic and therapeutic biomarkers, their utility in the management of patients with breast cancer, and current recommendations regarding their clinical use will be discussed.

[307]

**TÍTULO / TITLE:** - Long non-coding RNA HOTAIR is an independent prognostic marker of metastasis in estrogen receptor-positive primary breast cancer.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov 21.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10549-013-2776-7](#)

**AUTORES / AUTHORS:** - Sorensen KP; Thomassen M; Tan Q; Bak M; Cold S; Burton M; Larsen MJ; Kruse TA

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Genetics, Odense University Hospital, Sdr. Boulevard 29, 5000, Odense C, Denmark, [kristina.sorensen1@rsyd.dk](mailto:kristina.sorensen1@rsyd.dk).

**RESUMEN / SUMMARY:** - Expression of HOX transcript antisense intergenic RNA (HOTAIR)-a long non-coding RNA-has been examined in a variety of human cancers, and overexpression of HOTAIR is correlated with poor survival among breast, colon, and liver cancer patients. In this retrospective study, we examine HOTAIR expression in 164 primary breast tumors, from patients who do not receive adjuvant treatment, in a design that is paired with respect to the traditional prognostic markers. We show that HOTAIR expression differs between patients with or without a metastatic endpoint, respectively. Survival analysis shows that high HOTAIR expression in primary tumors is significantly associated with worse prognosis independent of prognostic markers (P = 0.012, hazard ratio (HR) 1.747). This association is even stronger when looking only

at estrogen receptor (ER)-positive tumor samples ( $P = 0.0086$ , HR 1.985). In ER-negative tumor samples, we are not able to detect a prognostic value of HOTAIR expression, probably due to the limited sample size. These results are successfully validated in an independent dataset with similar associations ( $P = 0.018$ , HR 1.825). In conclusion, our findings suggest that HOTAIR expression may serve as an independent biomarker for the prediction of the risk of metastasis in ER-positive breast cancer patients.

[308]

**TÍTULO / TITLE:** - Silencing MAP3K1 expression through RNA interference enhances paclitaxel-induced cell cycle arrest in human breast cancer cells.

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

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1007/s11033-013-2811-0](#)

**AUTORES / AUTHORS:** - Hu P; Huang Q; Li Z; Wu X; Ouyang Q; Chen J; Cao Y

**INSTITUCIÓN / INSTITUTION:** - Jiangxi Breast Center Third Hospital of Nanchang, Nanchang, 33009, China.

**RESUMEN / SUMMARY:** - The objective of this study is to compare the expression level of MAP3K1 between normal mammary gland cells and breast cancer cells, and to analyze the effects of silencing MAP3K1 on breast cancer cells with paclitaxel treatment. Western blotting analysis was used to detect the expression level of MAP3K1 in MCF-7 and MCF-12F cells. The effect of gene silencing through different siRNAs was determined by realtime-PCR. MTT assay was used to test the cell proliferation. Cell cycle was detected by flow cytometry. MAP3K1 protein expression level in breast cancer cells was higher than that in normal mammary gland cells. MAP3K1 siRNA transfection significantly reduced the expression level of MAP3K1, and enhanced paclitaxel-induced cell proliferation inhibition and cell cycle arrest in breast cancer cells. Targeting MAP3K1 expression through small RNA interference can promote the therapeutic effects of paclitaxel in breast cancer.

[309]

**TÍTULO / TITLE:** - Imaging of Epidermal Growth Factor Receptor Expression in Head and Neck Cancer with SPECT/CT and  $^{111}\text{In}$ -Labeled Cetuximab-F(ab')<sub>2</sub>.

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

**REVISTA / JOURNAL:** - J Nucl Med. 2013 Dec;54(12):2118-24. doi: 10.2967/jnumed.113.123612. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [2967/jnumed.113.123612](#)

**AUTORES / AUTHORS:** - van Dijk LK; Hoeben BA; Kaanders JH; Franssen GM; Boerman OC; Bussink J

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and.

**RESUMEN / SUMMARY:** - Combined treatment of advanced head and neck squamous cell carcinomas (HNSCC) with radiotherapy and the epidermal growth factor receptor (EGFR) inhibitor cetuximab improves clinical outcome in comparison to radiotherapy alone but is effective only in a few cases. To select those patients most likely to benefit from EGFR inhibition, it can be advantageous to quantify the tumor EGFR status

before and possibly during therapy. The aim of this study was to develop and characterize the (111)In-cetuximab-F(ab')<sub>2</sub> tracer to image EGFR targeting in vivo. METHODS: The affinity and internalization kinetics of (111)In-cetuximab-F(ab')<sub>2</sub> were determined in vitro. The optimal protein-fragment dose for imaging was determined in nude mice with a subcutaneous head and neck carcinoma model (FaDu). Mice with FaDu tumors were imaged using ultra-high-resolution SPECT with (111)In-cetuximab-F(ab')<sub>2</sub> or (111)In-cetuximab IgG at 4, 24, 48, and 168 h after injection. Tumor tracer uptake was determined on micro-SPECT and autoradiography images of tumor sections. Immunohistochemical staining was used to analyze EGFR expression in the tumor. RESULTS: In vitro, more than 50% of (111)In-cetuximab-F(ab')<sub>2</sub> was internalized into FaDu cells within 24 h. The half maximal inhibitory concentration (IC<sub>50</sub>) of (111)In-cetuximab-F(ab')<sub>2</sub> and (111)In-cetuximab was similar: 0.42 +/- 0.16 nM versus 0.28 +/- 0.14 nM, respectively. The protein dose-escalation study showed that the highest uptake of (111)In-cetuximab-F(ab')<sub>2</sub> in tumors was obtained at doses of 10 µg/mouse or less (13.5 +/- 5.2 percentage injected dose per gram [%ID/g]). Tumor uptake of (111)In-cetuximab was significantly higher (26.9 +/- 3.3 %ID/g, P < 0.01). However, because of rapid blood clearance, tumor-to-blood ratios at 24 h after injection were significantly higher for (111)In-cetuximab-F(ab')<sub>2</sub> (31.4 +/- 3.8 vs. 1.7 +/- 0.2, respectively; P < 0.001). The intratumoral distribution of (111)In-cetuximab-F(ab')<sub>2</sub> correlated well with the immunohistochemical distribution of EGFR (r = 0.64 +/- 0.06, P < 0.0001). micro-SPECT images of (111)In-cetuximab-F(ab')<sub>2</sub> clearly showed preferential uptake in the tumor from 4 h onward, with superior tumor-to-background contrast at 24 h, compared with (111)In-cetuximab (107.0 +/- 17.0 vs. 69.7 +/- 3.9, respectively; P < 0.05). CONCLUSION: (111)In-cetuximab-F(ab')<sub>2</sub> displays higher tumor-to-blood ratios early after injection than (111)In-cetuximab in an HNSCC model, making it more suitable for EGFR visualization and potentially for selecting patients for treatment with EGFR inhibitors.

[310]

**TÍTULO / TITLE:** - Risk factors for ocular surface squamous neoplasia recurrence following treatment with topical mitomycin C and interferon alpha-2b.

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

**REVISTA / JOURNAL:** - Am J Ophthalmol. 2013 Oct 31. pii: S0002-9394(13)00708-3. doi: 10.1016/j.ajo.2013.10.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.ajo.2013.10.012](#)

**AUTORES / AUTHORS:** - Besley J; Pappalardo J; Lee GA; Hirst LW; Vincent SJ

**INSTITUCIÓN / INSTITUTION:** - City Eye Centre, Brisbane, Queensland Australia.

**RESUMEN / SUMMARY:** - PURPOSE: To determine the rate of recurrence and associated risk factors following the use of mitomycin C (MMC) and/or interferon alpha-2b (IFN) for management of non-invasive ocular surface squamous neoplasia (OSSN). DESIGN: Retrospective non-comparative interventional case series. METHODS: Clinical practice setting of 135 patients treated consecutively with topical MMC (0.4 mg/mL) and/or IFN (1 million units/mL) for OSSN observed for clinical recurrence. RESULTS: Clinical recurrences were diagnosed in 19 of 135 (14.1%) eyes following topical treatment. The mean time to recurrence was 17.2 months (range 4 - 61) with 14 (73.7%) recurring within a two year period. There was no greater risk of recurrence identified for variables including lesion size, lesion location, gender, age, treatment type

or duration. Post-hoc log-Rank pairwise comparisons revealed that lesions initially treated using surgery alone had significantly reduced time to recurrence (21.1 +/- 5.6 months) compared to previous topical treatment with MMC (with or without surgery) (29.6 +/- 4.7 months) ( $p = 0.04$ ) and primary OSSN (23.2 +/- 1.8 months) ( $p = 0.09$ ). CONCLUSIONS: Topical MMC and IFN are an effective treatment modality for a wide range of non-invasive OSSN. Topical therapy avoids the morbidity of excisional surgery with equivalent or reduced recurrence rates and should be considered as primary therapy.

[311]

**TÍTULO / TITLE:** - Fibroblast growth factor receptor 4 polymorphism is associated with increased risk and poor prognosis of non-Hodgkin's lymphoma.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 19.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1386-7](#)

**AUTORES / AUTHORS:** - Gao L; Feng Z; Li Q; Li L; Chen L; Xiao T

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Liaocheng People's Hospital, Liaocheng, Shandong Province, 252000, China.

**RESUMEN / SUMMARY:** - Fibroblast growth factor receptor 4 (FGFR4) is expressed in various cell types and plays important roles in regulating immune responses. Evidence has shown that FGFR4 rs351855 (Gly388Arg) polymorphism may act as a risk factor for many diseases. In the current study, we investigated the association between FGFR4 polymorphisms and the susceptibility to non-Hodgkin's lymphoma (NHL) in the Chinese population. Two polymorphisms in the FGFR4 gene (rs351855G/A and rs147603016G/A) were detected by polymerase chain reaction-restriction fragment length polymorphism in 421 NHL cases and 486 healthy controls. Results showed that prevalence of rs351855AA genotype was significantly increased in patients than in controls (odds ratio [OR] = 2.02, 95 % confidence interval [CI] 1.91-3.23,  $P < 0.001$ ). Similarly, rs351855A allele presented significantly higher numbers in cases compared to healthy donors (49.8 versus 40.1 %,  $P < 0.001$ ). Further study revealed that the frequency of the rs351855G/A polymorphism was clearly elevated in cases with B cell subtype than those with T cell subtypes. When analyzing the survival time of NHL patients with FGFR4 rs351855G/A polymorphism, cases with AA genotype had significantly shorter survival time compared to the patients with GG genotype ( $P < 0.001$ ) or GA genotype ( $P < 0.001$ ). These results suggest that FGFR4 rs351855G/A polymorphism is associated with increased susceptibility to NHL and could be used as a marker for predicting the prognosis of the malignancy.

[312]

**TÍTULO / TITLE:** - C1q tumor necrosis factor-related protein-3 protects mesenchymal stem cells against hypoxia- and serum deprivation-induced apoptosis through the phosphoinositide 3-kinase/Akt pathway.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2014 Jan;33(1):97-104. doi: 10.3892/ijmm.2013.1550. Epub 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1550](#)

**AUTORES / AUTHORS:** - Hou M; Liu J; Liu F; Liu K; Yu B

**INSTITUCIÓN / INSTITUTION:** - The Key Laboratory of Myocardial Ischemia, Harbin Medical University, Ministry of Education, Heilongjiang Province, P.R. China.

**RESUMEN / SUMMARY:** - Bone marrow (BM)-derived mesenchymal stem cells (MSCs) represent the leading candidate cell for tissue regeneration in the ischemic myocardium. However, the poor survival of stem cells transplanted into the ischemic myocardium presents a major obstacle in stem cell-based therapy. C1q tumor necrosis factor-related protein 3 (CTRP3) is a newly identified adipokine, similar to adiponectin, with beneficial effects on metabolic regulation. It has been shown to enhance the survival of cardiomyocytes during ischemia, while its expression is reduced following ischemia. In the present study, we examined the hypothesis that CTRP3 may enhance the survival of MSCs during exposure to hypoxia/serum deprivation (SD), and attempted to elucidate the underlying mechanisms. MSCs were obtained from rat bone marrow and cultured. Apoptosis was induced by hypoxia/SD for up to 24 h and the apoptotic rates were assessed by flow cytometry. MSC proliferation was measured using a Cell Counting kit-8 assay. The expression levels of Akt, Bcl-2, Bax, cytochrome c and cleaved caspase-3 were detected by western blot analysis. Mitochondrial membrane potential was examined using a membrane-permeable dye. CTRP3 significantly reduced hypoxia/SD-induced apoptosis in a concentration-dependent manner. The hypoxia/SD-induced decrease in the Bcl-2/Bax ratio and the mitochondrial membrane potential, and the increase in cytochrome c and caspase-3 levels were largely reversed by CTRP3. The anti-apoptotic effects of CTRP3 were blocked by inhibiting the activation of phosphoinositide 3-kinase (PI3K)/Akt signaling pathway with the PI3K inhibitor, LY294002. In conclusion, CTRP3 is a novel anti-apoptotic adipokine that protects MSCs from hypoxia/SD-induced apoptosis through the PI3K/Akt signaling pathway.

[313]

**TÍTULO / TITLE:** - Single nucleotide polymorphism array karyotyping: A diagnostic and prognostic tool in myelodysplastic syndromes with unsuccessful conventional cytogenetic testing.

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

**REVISTA / JOURNAL:** - Genes Chromosomes Cancer. 2013 Oct 7. doi: 10.1002/gcc.22112.

●● Enlace al texto completo (gratis o de pago) [1002/gcc.22112](#)

**AUTORES / AUTHORS:** - Arenillas L; Mallo M; Ramos F; Guinta K; Barragan E; Lumbreras E; Larrayoz MJ; De Paz R; Tormo M; Abaigar M; Pedro C; Cervera J; Such E; Jose Calasanz M; Diez-Campelo M; Sanz GF; Hernandez JM; Luno E; Saumell S; Maciejewski J; Florensa L; Sole F

**INSTITUCIÓN / INSTITUTION:** - Laboratori de Citologia Hematologica. Laboratori de Citogenetica Molecular, Pathology Department, Hospital del Mar, GRETNHE, IMIM (Hospital del Mar Research Institute), Barcelona, España.

**RESUMEN / SUMMARY:** - Cytogenetic aberrations identified by metaphase cytogenetics (MC) have diagnostic, prognostic, and therapeutic implications in myelodysplastic syndromes (MDS). However, in some MDS patients MC study is unsuccessful. Single nucleotide polymorphism array (SNP-A) based karyotyping could be helpful in these cases. We performed SNP-A in 62 samples from bone marrow or

peripheral blood of primary MDS with an unsuccessful MC study. SNP-A analysis enabled the detection of aberrations in 31 (50%) patients. We used the copy number alteration information to apply the International Prognostic Scoring System (IPSS) and we observed differences in survival between the low/intermediate-1 and intermediate-2/high risk patients. We also saw differences in survival between very low/low/intermediate and the high/very high patients when we applied the revised IPSS (IPSS-R). In conclusion, SNP-A can be used successfully in PB samples and the identification of CNA by SNP-A improve the diagnostic and prognostic evaluation of this group of MDS patients. © 2013 Wiley Periodicals, Inc.

[314]

**TÍTULO / TITLE:** - Estrogen receptor beta upregulates FOXO3a and causes induction of apoptosis through PUMA in prostate cancer.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Sep 30. doi: 10.1038/onc.2013.384.

●● [Enlace al texto completo \(gratis o de pago\) 1038/onc.2013.384](#)

**AUTORES / AUTHORS:** - Dey P; Strom A; Gustafsson JA

**INSTITUCIÓN / INSTITUTION:** - Department of Biology and Biochemistry, Center for Nuclear Receptors and Cell Signaling, University of Houston, Houston, TX, USA.

**RESUMEN / SUMMARY:** - Estrogen receptor beta (ERbeta) is emerging as a critical factor in understanding prostate cancer biology. Although reduced in prostate cancer above Gleason grade 3, ERbeta is a potential drug target at the initial stage of the disease. In human prostate cancer cells, we found that ERbeta causes apoptosis by increasing the expression of pro-apoptotic factor p53-upregulated modulator of apoptosis (PUMA), independent of p53, but dependent on the forkhead transcription factor class-O family member, FOXO3a. FOXO3a has previously been shown to induce PUMA after growth factor withdrawal and inhibition of the Akt pathway. Surprisingly, the phosphorylation of FOXO3a remained unchanged, while the mRNA and total protein levels of FOXO3a were increased in response to ERbeta expression or treatment of PC3, 22Rv1 and LNCaP cells with the ERbeta-specific ligands 3beta-Adiol (5alpha-androstane-3beta,17beta-diol), DPN (diarylpropionitrile) or 8beta-VE2 (8-vinylestra-1,3,5 (10)-triene-3,17beta-diol). Knockdown of FOXO3a or ERbeta expression abolished the increase of PUMA in response to 3beta-Adiol in LNCaP and PC3 cells, suggesting that FOXO3a mediates the apoptotic effect of 3beta-Adiol-activated ERbeta. Moreover, the ventral prostate of ERbeta-/- mice had decreased expression of FOXO3a and PUMA compared with the ERbeta+/+ mice, indicating a relationship between ERbeta and FOXO3a expression. The regulation of FOXO3a by ERbeta in normal basal epithelial cells indicates a function of ERbeta in cell differentiation and maintenance of cells in a quiescent state. In addition, the expression of ERbeta, FOXO3a and PUMA is comparable and higher in benign prostatic hyperplasia than in prostate cancer Gleason grade 4 or higher, where there is substantial loss of ERbeta, FOXO3a and PUMA. We conclude that ERbeta induces apoptosis of prostate cancer cells by increasing transcription of FOXO3a, leading to an increase of PUMA and subsequent triggering of apoptosis via the intrinsic pathway involving caspase-9. Furthermore, we conclude that ligands specifically activating ERbeta could be useful pharmaceuticals in the treatment of prostate cancer. Oncogene advance online publication, 30 September 2013; doi:10.1038/onc.2013.384.

[315]

**TÍTULO / TITLE:** - Expression of cell cycle regulatory proteins in eyelid sebaceous gland carcinoma: Low p27 expression predicts poor prognosis.

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

**REVISTA / JOURNAL:** - Exp Eye Res. 2013 Nov 8. pii: S0014-4835(13)00311-4. doi: 10.1016/j.exer.2013.10.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.exer.2013.10.022](#)

**AUTORES / AUTHORS:** - Kim N; Kim JE; Choung HK; Lee MJ; Khwang SI

**INSTITUCIÓN / INSTITUTION:** - Department of Ophthalmology, Seoul National University College of Medicine, Seoul, South Korea; Department of Ophthalmology, Seoul National University Bundang Hospital, Seongnam, South Korea.

**RESUMEN / SUMMARY:** - Prognosis of eyelid sebaceous gland carcinoma is largely unpredictable and there are few practically available markers for predicting patients' prognosis. Dysregulation of cell cycle progression is strongly associated with the development of cancer and the cancer prognosis. We investigated the expression of cell cycle regulatory proteins in eyelid sebaceous gland carcinoma and estimate their value as prognostic predictors. Forty-three cases of eyelid sebaceous gland carcinoma were included in this study. Immunohistochemistry for the p53, p21, p27, cyclin E, p16, cyclin D1, and phosphorylated Rb (pRb) proteins was performed using archival paraffin blocks. Correlations between clinical features and protein expression were evaluated statistically. Nine patients showed lymph node or distant metastasis, and the remaining patients showed localized disease. High expression of p21, p27, cyclin E, and p16 was found in the majority of tumor cell nuclei, whereas these proteins were rarely expressed in the normal sebaceous glands. However, pRb was focally lost in a subset of cases. Patients showing diffuse p27 expression developed metastasis less commonly than those with negative or focal p27 expression (log-rank test,  $p = 0.008$ ). Aberrant expression of cell cycle regulatory proteins was observed in eyelid sebaceous gland carcinoma, suggesting that cell cycle dysregulation is involved in the pathogenesis of this tumor. Decreased p27 expression is a predictive biomarker of an unfavorable prognosis of eyelid sebaceous gland carcinoma.

[316]

**TÍTULO / TITLE:** - Scoring System for Predicting Recurrence after Chemoradiotherapy Including 5-Fluorouracil and Platinum for Patients with Esophageal Cancer.

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

**REVISTA / JOURNAL:** - Hepatogastroenterology. 2013 Oct 2;60(128). doi: 10.5754/hge13131.

●● Enlace al texto completo (gratis o de pago) [5754/hge13131](#)

**AUTORES / AUTHORS:** - Kogo M; Suzuki A; Sunaga T; Kaneko K; Yoneyama K; Imawari M; Kiuchi Y

**RESUMEN / SUMMARY:** - Background/Aims: We have retrospectively evaluated clinical data obtained before therapy to enable reliable prediction of recurrence after chemoradiotherapy (CRT) for esophageal cancer. Methodology: We analyzed 108 patients who received 5-fluorouracil and platinum combined with 60 Gy radiation. Of the 108 patients, 42 patients with complete response after CRT were selected for this

study. The endpoint was recurrence after CRT. Factors significantly related to recurrence were extracted by the multivariate analysis, and a recurrence score was prepared by combining these factors. Results: The median follow-up interval was 18.5 (2-103) months. Recurrent disease was found in 16 (38.1%) patients. In the univariate analysis, recurrence was associated with nutrition status, family history, dysphagia, location, and length of the tumor. In the multivariate analysis, location of the tumor was selected as a significant factor that contributed independently to recurrence after CRT ( $p < 0.05$ ). The hazard ratios of the five selected factors was approximated and scored. The cumulative probabilities of tumor recurrence were significantly higher in the high score group than in the low score group (47.5% vs. 12.5% at 6 months,  $p < 0.01$ ). Conclusions: The recurrence score is suggested to be an appropriate scoring system with which to predict recurrence in patients with esophageal cancer.

[317]

**TÍTULO / TITLE:** - A myelopoiesis gene signature during remission in ANCA associated vasculitis does not predict relapses but seems to reflect ongoing prednisolone therapy.

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

**REVISTA / JOURNAL:** - Clin Exp Immunol. 2013 Nov 11. doi: 10.1111/cei.12236.

●● [Enlace al texto completo \(gratis o de pago\) 1111/cei.12236](#)

**AUTORES / AUTHORS:** - Kurz T; Weiner M; Skoglund C; Basnet S; Eriksson P; Segelmark M

**INSTITUCIÓN / INSTITUTION:** - Department of Medical and Health Sciences, Linköping University, Linköping, Sweden.

**RESUMEN / SUMMARY:** - A myelopoiesis gene signature in circulating leucocytes, exemplified by increased myeloperoxidase (MPO) and proteinase 3 (PR3) mRNA levels, has been reported in patients with active anti-neutrophil cytoplasm antibody associated vasculitis (AAV) and to a lesser extent during remission. We hypothesized that this signature could predict disease relapse. mRNA levels of PR3, MPO, selected myelopoiesis transcription factors (CEBPA, CEBPB, SPIB, SPI1) and microRNAs (miRNAs) from patient and control peripheral blood mononuclear cells (PBMCs) and polymorphonuclear cells (PMNs) were analyzed and associated with clinical data. Patients in stable remission had higher mRNA levels for PR3 (PBMCs, PMNs) and MPO (PBMCs). PR3 and SPIB mRNA correlated positively in control but negatively in patient PBMCs. Statistically significant correlations existed between PR3 mRNA and several miRNAs in controls, but not in patients. PR3/MPO mRNA levels were not associated with previous or future relapses but correlated to steroid treatment. Prednisolone doses were negatively linked to SPIB and miR-155-5p, miR-339-5p (PBMCs) and to miR-221, miR-361, miR-505 (PMNs). PR3 mRNA in PBMCs correlated with time since last flare, blood leucocyte count and estimated glomerular filtration rate. Our results show that elevated leucocyte PR3 mRNA levels in AAV patients in remission do not predict relapse. The origin seems multifactorial, but to an important part explainable by prednisolone action. Gene signatures in patients with AAV undergoing steroid treatment should therefore be interpreted accordingly.

[318]

**TÍTULO / TITLE:** - Arsenic trioxide induces apoptosis in B-cell chronic lymphocytic leukemic cells through down-regulation of survivin via the p53-dependent signaling pathway.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Dec;37(12):1719-25. doi: 10.1016/j.leukres.2013.09.019. Epub 2013 Sep 29.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.09.019](#)

**AUTORES / AUTHORS:** - Zhang XH; Feng R; Lv M; Jiang Q; Zhu HH; Qing YZ; Bao JL; Huang XJ; Zheng XL

**INSTITUCIÓN / INSTITUTION:** - Peking University People's Hospital, Peking University Institute of Hematology, Beijing 100044, China. Electronic address: [zhangxh100@sina.com](mailto:zhangxh100@sina.com).

**RESUMEN / SUMMARY:** - Arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) can induce apoptosis in many tumors. However, the associated mechanisms are not clearly understood. We found that As<sub>2</sub>O<sub>3</sub> significantly inhibited the proliferation of WSU-CLL cells and induced apoptosis in dose- and time-dependent manners. WSU-CLL cells treated with 2μM As<sub>2</sub>O<sub>3</sub> showed survivin down-regulation and p53 up-regulation. Survivin siRNA combined with As<sub>2</sub>O<sub>3</sub> further inhibited the proliferation of WSU-CLL cells. p53 inhibition by siRNA prevented the down-regulation of survivin by As<sub>2</sub>O<sub>3</sub> and prevented the As<sub>2</sub>O<sub>3</sub>-induced cytotoxicity of WSU-CLL cells. These results suggest that As<sub>2</sub>O<sub>3</sub> may be of therapeutic value for chronic lymphocytic leukemia.

[319]

**TÍTULO / TITLE:** - ROS and RNS induced apoptosis through p53 and iNOS mediated pathway by a dibasic hydroxamic acid molecule in leukemia cells.

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

**REVISTA / JOURNAL:** - Eur J Pharm Sci. 2013 Nov 21. pii: S0928-0987(13)00448-X. doi: 10.1016/j.ejps.2013.11.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejps.2013.11.009](#)

**AUTORES / AUTHORS:** - Banerjee K; Ganguly A; Chakraborty P; Sarkar A; Singh S; Chatterjee M; Bhattacharya S; Choudhuri SK

**INSTITUCIÓN / INSTITUTION:** - Department of In Vitro Carcinogenesis and Cellular Chemotherapy, Chittaranjan National Cancer Institute, Kolkata, India.

**RESUMEN / SUMMARY:** - Anticancer drugs induce apoptosis to cancer cells and also exhibit undesired toxicity to normal cells. Therefore development of novel agents triggering apoptosis and have low toxicity towards normal cells is most important. Hydroxamic acids suppress tumour cell growth through apoptosis but the underlying mechanism is poorly understood. Herein, we describe the apoptotic potential of a dibasic hydroxamic acid derivative, viz., oxalyl bis (Nphenyl) hydroxamic acid (OBPHA), which induces apoptosis through generation of both ROS and NO in doxorubicin resistant T-lymphoblastic leukemia, CEM/ADR5000 cells. Present study discloses that OBPHA selectively kills cancerous cells irrespective of their drug resistant phenotype. We also determined the crystal structure of OBPHA to understand the structural requirements for apoptosis; the study reveals that the presence of substituted hydroxamic acid groups (-CO-NH-OH) favours the generation of NO possibly through auto degeneration. Along with the induction of caspase 3 mediated intrinsic apoptosis; OBPHA also activates p53 dependent signalling cascade and downregulates HDAC3

expression in a time dependent manner possibly due to increased ROS and NO production and simultaneous decrease in cellular GSH level. Thus ROS and NO mediated downstream signalling are essential for the anticancer effect of OBPHA. Therefore OBPHA, having a structurally relevant pharmacophore provides important insight into the development of new ROS and RNS generating chemicals inducing p53 dependent apoptosis.

[320]

**TÍTULO / TITLE:** - Intermittent versus continuous erlotinib with concomitant modified "XELOX" (q3W) in first-line treatment of metastatic colorectal cancer: Correlation With Serum Amphiregulin and Transforming Growth Factor Alpha.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Dec 1;119(23):4145-53. doi: 10.1002/cncr.28327. Epub 2013 Oct 1.

●● [Enlace al texto completo \(gratis o de pago\) 1002/cncr.28327](#)

**AUTORES / AUTHORS:** - Ma BB; Chan SL; Ho WM; Lau W; Mo F; Hui EP; Chan C; Poon A; Dattatray RD; Wong SC; To KF; King AD; Ahuja A; Chan AT

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, Sir Y.K. Pao Centre for Cancer, State Key Laboratory in Oncology in South China, Hong Kong Cancer Institute and Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, Hong Kong SAR, China.

**RESUMEN / SUMMARY:** - BACKGROUND: This study evaluated the activity of 2 schedules of erlotinib in combination with chemotherapy, and the prognostic significance of serum amphiregulin (AREG) and transforming growth factor alpha (TGFA) in metastatic colorectal cancer. METHODS: A total of 60 untreated patients were randomized to a "continuous" (CON; erlotinib 100 mg daily) or an "intermittent" (INT; erlotinib 150 mg on alternate day on day 2 to 14, then 150 mg daily on days 15 to 21) schedule of erlotinib with a modified XELOX (capecitabine plus oxaliplatin) regimen. Serum levels of AREG and TGFA were determined serially. RESULTS: Baseline characteristics were similar between the 2 arms. Of the 58 patients evaluated for response, there was a nonsignificant trend toward a slightly higher overall response rate in the INT arm (66.7%) versus the CON arm (56.7%). At a median follow-up of 2.8 years, the median overall survival was 18.8 months (95% confidence interval = 11.3-22.9 months) and 20.7 months (95% confidence interval = 12.5-31 months, P = .19) for the CON and INT arm, respectively. KRAS mutation did not predict drug response. The 2 arms did not differ significantly in toxicity. Baseline serum TGFA was an independent predictor of progression-free survival, whereas a drop in serum TGFA and AREG levels following 3 to 4 cycles of treatment were associated with shorter progression-free survival and overall survival, respectively. CONCLUSIONS: The intermittent erlotinib schedule was associated with a higher response rate, although this is not statistically significant. Serum TGFA and AREG levels have prognostic significance in erlotinib-treated patients with colorectal cancer, and further studies are warranted. Cancer 2013;119:4145-4153. © 2013 American Cancer Society.

[321]

**TÍTULO / TITLE:** - MiR-125b acts as an oncogene in glioblastoma cells and inhibits cell apoptosis through p53 and p38MAPK-independent pathways.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2853-63. doi: 10.1038/bjc.2013.672. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.672](#)

**AUTORES / AUTHORS:** - Wu N; Lin X; Zhao X; Zheng L; Xiao L; Liu J; Ge L; Cao S

**INSTITUCIÓN / INSTITUTION:** - Institute of Oceanology, Chinese Academy of Sciences, Qingdao 266071, China.

**RESUMEN / SUMMARY:** - Background: We have recently identified miR-125b upregulation in glioblastoma (GMB). The aim of this study is to determine the correlation between miR-125b expression and malignant grades of glioma and the genes targeted by miR-125b. Methods: Real-time PCR was employed to measure the expression level of miR-125b. Cell viability was evaluated by cell growth and colony formation in soft-agar assays. Cell apoptosis was determined by Hoechst 33342 staining and AnnexinV-FITC assay. The Luciferase assay was used to confirm the actual binding sites of p38MAPK mRNA. Western blot was used to detect the gene expression level. Results: The expression level of miR-125b is positively correlated with the malignant grade of glioma. Ectopic expression of miR-125b promotes the proliferation of GMB cells. Knockdown of endogenous miR-125b inhibits cell proliferation and promotes cell apoptosis. Further studies reveal that p53 is regulated by miR-125b. However, downregulation of the endogenous miR-125b also results in p53-independent apoptotic pathway leading to apoptosis in p53 mutated U251 cells and p53 knockdown U87 cells. Moreover, p38MAPK is also regulated by miR-125b and downregulation of miR-125b activates the p38MAPK-induced mitochondria apoptotic pathway. Conclusion: High-level expression of miR-125b is associated with poor outcomes of GMB. MiR-125b may have an oncogenic role in GMB cells by promoting cell proliferation and inhibiting apoptosis.

[322]

**TÍTULO / TITLE:** - MiR-365 induces gemcitabine resistance in pancreatic cancer cells by targeting the adaptor protein SHC1 and pro-apoptotic regulator BAX.

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

**REVISTA / JOURNAL:** - Cell Signal. 2013 Nov 9;26(2):179-185. doi: 10.1016/j.cellsig.2013.11.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.cellsig.2013.11.003](#)

**AUTORES / AUTHORS:** - Hamada S; Masamune A; Miura S; Satoh K; Shimosegawa T

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1, Seiryomachi, Aobaku, Sendai City, Miyagi 980-8574, Japan. Electronic address: [hamadas@med.tohoku.ac.jp](mailto:hamadas@med.tohoku.ac.jp).

**RESUMEN / SUMMARY:** - The poor prognosis of invasive ductal adenocarcinoma of the pancreas is mainly due to its resistance against therapeutic agents. The molecular mechanism by which morbidity enhances cell survival has been extensively studied, but radical improvements in the therapeutic strategy have not yet been achieved. Recent reports have indicated the substantial contribution of miRNA in multiple cell functions by comprehensively targeting clusters of genes. We identified several miRNAs highly expressed in invasive ductal adenocarcinoma in our previous study,

and clarified their contribution to the epithelial-mesenchymal transition. Among the differentially expressed miRNAs, miR-365 was highly expressed in invasive ductal adenocarcinoma, whose functional role has not been reported. In the current study, we found that miR-365 induced gemcitabine resistance in pancreatic cancer cells. MiR-365 directly targeted adaptor protein Src Homology 2 Domain Containing 1 (SHC1) and apoptosis-promoting protein BAX. The siRNA-based knockdown of SHC1 and BAX increased gemcitabine resistance, indicating the miR-365/SHC1/BAX axis influences the survival of pancreatic cancer cells. In addition, miR-365 up-regulated cancer-promoting molecules such as Inhibitor of DNA binding 2 and S100P, suggesting the existence of cross-talk with other cancer-promoting signals. MiR-365 could exert orchestrated effects on pancreatic cancer cell survival.

[323]

**TÍTULO / TITLE:** - Arsenic Trioxide in Front-line Therapy of Acute Promyelocytic Leukemia (C9710): Prognostic Significance of FLT3 Mutations and Complex Karyotype.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Oct 28.

- Enlace al texto completo (gratis o de pago) [3109/10428194.2013.842985](#)

**AUTORES / AUTHORS:** - Poire X; Moser BK; Gallagher RE; Laumann K; Bloomfield CD; Powell BL; Koval G; Gulati K; Holowka N; Larson RA; Tallman MS; Appelbaum FR; Sher D; Willman C; Paietta E; Stock W

**RESUMEN / SUMMARY:** - Abstract The addition of arsenic trioxide (ATO) to frontline therapy of acute promyelocytic leukemia (APL) has been shown to result in significant improvements in disease-free survival (DFS). FLT3 mutations are frequently observed in APL but its prognostic significance remains unclear. We analyzed 245 newly diagnosed adult patients with APL treated on intergroup trial C9710 and evaluated previously defined biological and prognostic factors and their relationship to FLT3 mutations and to additional karyotypic abnormalities. FLT3 mutations were found in 48% of patients, including 31% with an internal tandem duplication (FLT3-ITD), 14% with a point mutation (FLT3-D835) and 2% with both mutations. The FLT3-ITD mutant level was uniformly low, <0.5. Neither FLT3 mutations had an impact on remission rate, induction death rate, DFS or overall survival (OS). The addition of ATO consolidation improved outcomes regardless of FLT3 mutation type or level, initial white blood cell count, PML-RARA isoform type or transcript level. The presence of a complex karyotype was strongly associated with an inferior OS independently of post-remission treatment. In conclusion, the addition of ATO to frontline therapy overcomes the impact of previously described adverse prognostic factors including FLT3 mutations. However, complex karyotype is strongly associated with an inferior OS despite ATO therapy.

[324]

**TÍTULO / TITLE:** - Single-strand selective monofunctional uracil-DNA glycosylase (SMUG1) deficiency is linked to aggressive breast cancer and predicts response to adjuvant therapy.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov 20.

- Enlace al texto completo (gratis o de pago) [1007/s10549-013-2769-6](https://doi.org/10.1007/s10549-013-2769-6)

**AUTORES / AUTHORS:** - Abdel-Fatah TM; Albarakati N; Howell L; Agarwal D; Moseley P; Hawkes C; Ball G; Chan S; Ellis IO; Madhusudan S

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Nottingham University Hospitals, Nottingham, NG51PB, UK.

**RESUMEN / SUMMARY:** - Uracil in DNA is an important cause of mutagenesis. SMUG1 is a uracil-DNA glycosylase that removes uracil through base excision repair. SMUG1 also processes radiation-induced oxidative base damage as well as 5-fluorouracil incorporated into DNA during chemotherapy. We investigated SMUG1 mRNA expression in 249 primary breast cancers. SMUG1 protein expression was investigated in 1,165 breast tumours randomised into two cohorts [training set (n = 583) and test set (n = 582)]. SMUG1 and chemotherapy response was also investigated in a series of 315 ER-negative tumours (n = 315). For mechanistic insights, SMUG1 was correlated to biomarkers of aggressive phenotype, DNA repair, cell cycle and apoptosis. Low SMUG1 mRNA expression was associated with adverse disease specific survival (p = 0.008) and disease-free survival (p = 0.008). Low SMUG1 protein expression (25 %) was associated with high histological grade (p < 0.0001), high mitotic index (p < 0.0001), pleomorphism (p < 0.0001), glandular de-differentiation (p = 0.0001), absence of hormonal receptors (ER-/PgR-/AR) (p < 0.0001), presence of basal-like (p < 0.0001) and triple-negative phenotypes (p < 0.0001). Low SMUG1 protein expression was associated with loss of BRCA1 (p < 0.0001), ATM (p < 0.0001) and XRCC1 (p < 0.0001). Low p27 (p < 0.0001), low p21 (p = 0.023), mutant p53 (p = 0.037), low MDM2 (p < 0.0001), low MDM4 (p = 0.004), low Bcl-2 (p = 0.001), low Bax (p = 0.003) and high MIB1 (p < 0.0001) were likely in low SMUG1 tumours. Low SMUG1 protein expression was associated with poor prognosis in univariate (p < 0.001) and multivariate analysis (p < 0.01). In ER+ cohort that received adjuvant endocrine therapy, low SMUG1 protein expression remains associated with poor survival (p < 0.01). In ER- cohort that received adjuvant chemotherapy, low SMUG1 protein expression is associated with improved survival (p = 0.043). Our study suggests that low SMUG1 expression may correlate to adverse clinicopathological features and predict response to adjuvant therapy in breast cancer.

[325]

**TÍTULO / TITLE:** - MET Gene Copy Number Gain is an Independent Poor Prognostic Marker in Korean Stage I Lung Adenocarcinomas.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Nov 9.

- Enlace al texto completo (gratis o de pago) [1245/s10434-013-3355-1](https://doi.org/10.1245/s10434-013-3355-1)

**AUTORES / AUTHORS:** - Jin Y; Sun PL; Kim H; Seo AN; Jheon S; Lee CT; 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: MET gene copy number gain (CNG) and protein overexpression have been reported in lung cancer, but the clinical implications in early stage adenocarcinoma remain unclear. METHODS: We investigated MET gene copy number and protein expression in 141 cases of surgically resected stage I pulmonary adenocarcinoma. MET gene CNG was determined by silver in situ

hybridization, and MET protein expression was assessed by immunohistochemistry. The correlation between MET gene CNG/protein expression and clinicopathologic parameters and prognostic significance was analyzed. RESULTS: MET gene CNG was found in 24.1 % (34 of 141) of the cases and was associated with larger tumor size, pleural invasion, and lymphatic vessel invasion. MET gene CNG was inversely correlated with the presence of lepidic subtype ( $r = -0.17$ ,  $p = 0.045$ ) and was not associated with EGFR, KRAS mutation, or ALK gene rearrangement. In addition, MET gene CNG was significantly associated with shorter disease-free survival (DFS) (49 vs. 75 months;  $p < 0.001$ ) and shorter overall survival (OS) (65 vs. 78 months;  $p = 0.01$ ). Multivariate analysis confirmed that MET gene CNG was significantly associated with poorer DFS [ $p < 0.001$ ; hazard ratio (HR) 5.5; 95 % confidence interval (CI) 2.2-13.9] but was not significantly associated with OS. MET overexpression was observed in 71.3 % of cases (97 of 136), but it was not correlated with gene CNG. CONCLUSIONS: MET gene CNG is an independent poor prognostic factor in patients with stage I lung adenocarcinoma. It is associated with aggressive pathologic features and is inversely correlated with the presence of lepidic subtype.

[326]

**TÍTULO / TITLE:** - The natural anticancer compound rocaglamide selectively inhibits the G1-S-phase transition in cancer cells through the ATM/ATR-mediated Chk1/2 cell cycle checkpoints.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 6. doi: 10.1002/ijc.28521.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ijc.28521](#)

**AUTORES / AUTHORS:** - Neumann J; Boerries M; Kohler R; Giaisi M; Krammer PH; Busch H; Li-Weber M

**INSTITUCIÓN / INSTITUTION:** - Tumorimmunology Program (D030), German Cancer Research Center (DKFZ), Heidelberg, Germany.

**RESUMEN / SUMMARY:** - Targeting the cancer cell cycle machinery is an important strategy for cancer treatment. Cdc25A is an essential regulator of cycle progression and checkpoint response. Over-expression of Cdc25A occurs often in human cancers. In this study, we show that Rocaglamide-A (Roc-A), a natural anticancer compound isolated from the medicinal plant Aglaia, induces a rapid phosphorylation of Cdc25A and its subsequent degradation and, thereby, blocks cell cycle progression of tumor cells at the G1-S phase. Roc-A has previously been shown to inhibit tumor proliferation by blocking protein synthesis. In this study, we demonstrate that besides the translation inhibition Roc-A can induce a rapid degradation of Cdc25A by activation of the ATM/ATR-Chk1/Chk2 checkpoint pathway. However, Roc-A has no influence on cell cycle progression in proliferating normal T lymphocytes. Investigation of the molecular basis of tumor selectivity of Roc-A by a time-resolved microarray analysis of leukemic vs. proliferating normal T lymphocytes revealed that Roc-A activates different sets of genes in tumor cells compared with normal cells. In particular, Roc-A selectively stimulates a set of genes responsive to DNA replication stress in leukemic but not in normal T lymphocytes. These findings further support the development of Rocaglamide for antitumor therapy.

[327]

**TÍTULO / TITLE:** - Overexpression of the circadian clock gene Bmal1 increases sensitivity to oxaliplatin in colorectal cancer.

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

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

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0171](#)

**AUTORES / AUTHORS:** - Zeng ZL; Luo HY; Yang J; Wu WJ; Chen DL; Huang P; Xu RH

**INSTITUCIÓN / INSTITUTION:** - Department of Research, Sun Yat-Sen University Cancer Center.

**RESUMEN / SUMMARY:** - PURPOSE: The circadian clock gene Bmal1 is involved in cancer cell proliferation and DNA damage sensitivity. The aim of this study was to explore the effect of Bmal1 on oxaliplatin sensitivity and to determine its clinical significance in colorectal cancer (CRC). EXPERIMENTAL DESIGN: Three CRC cell lines, HCT116, THC8307 and HT29, were used. The Bmal1-mediated control of CRC cell proliferation was tested in vitro and in vivo. MTT and colony formation assays were performed to determine the sensitivity of CRC cells to oxaliplatin. Flow cytometry was used to examine changes in the cell cycle distribution and apoptosis rate. Proteins expressed downstream of Bmal1 upon its overexpression were determined by Western blotting. Immunohistochemistry was used to analyze Bmal1 expression in 82 archived CRC tumors from patients treated with oxaliplatin-based regimens. RESULTS: Bmal1 overexpression inhibited CRC cell proliferation and increased CRC sensitivity to oxaliplatin in three CRC cell lines and HCT116 cells model in vivo. Furthermore, the overall survival of CRC patients with high Bmal1 levels in their primary tumors was significantly longer than that of patients with low Bmal1 levels (27 vs. 19 months;  $p=0.043$ ). The progression free survival of patients with high Bmal1 expression was also significantly longer than that of patients with low Bmal1 expression (11 vs. 5 months;  $p=0.015$ ). Mechanistically, the effect of Bmal1 was associated with its ability to regulate G2/M arrest by activating the ATM pathway. CONCLUSION: Bmal1 shows the potential as a novel prognostic biomarker and may represent a new therapeutic target in CRC.

[328]

**TÍTULO / TITLE:** - Can shear-wave elastography predict response to neoadjuvant chemotherapy in women with invasive breast cancer?

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2798-802. doi: 10.1038/bjc.2013.660. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.660](#)

**AUTORES / AUTHORS:** - Evans A; Armstrong S; Whelehan P; Thomson K; Rauchhaus P; Purdie C; Jordan L; Jones L; Thompson A; Vinnicombe S

**INSTITUCIÓN / INSTITUTION:** - Dundee Cancer Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK.

**RESUMEN / SUMMARY:** - Background: Response of invasive breast cancer to neoadjuvant chemotherapy (NAC) is variable, and prediction of response is imperfect. We aimed to ascertain whether tissue stiffness in breast cancers, as assessed by

shear-wave elastography (SWE) before treatment, is associated with response. Methods: We retrospectively compared pre-treatment tumour mean tissue stiffness, with post-treatment Residual Cancer Burden (RCB) scores and its components in 40 women with breast cancer treated by NAC using Pearson's correlation coefficient (CC), a general linear model and multiple linear regression. Subgroup analysis was carried out for luminal, HER2-positive and basal immunohistochemical subtypes. Results: Statistically significant correlations were shown between stiffness and RCB scores and between stiffness and percentage tumour cellularity. The correlation between stiffness and percentage cellularity was strongest (CC 0.35 (P<0.0001) compared with CC 0.23 (P=0.004) for the RCB score). The results of a general linear model show that cellularity and RCB score maintain independent relationships with stiffness. By multiple linear regression, only cellularity maintained a significant relationship with stiffness. Conclusion: Pre-treatment tumour stiffness measured by SWE, has a statistically significant relationship with pathological response of invasive breast cancer to NAC.

[329]

**TÍTULO / TITLE:** - Quantitative ER and PgR Assessment as Predictors of Benefit From Lapatinib in Postmenopausal Women With Hormone Receptor-Positive, HER-2 Negative Metastatic Breast Cancer.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 6.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-1260](#)

**AUTORES / AUTHORS:** - Finn RS; Press MF; Dering J; O'Rourke L; Florance A; Ellis CE; Martin AM; Johnston S

**INSTITUCIÓN / INSTITUTION:** - Div Hematology- Oncology, Geffen School of Medicine at UCLA.

**RESUMEN / SUMMARY:** - PURPOSE: Lapatinib, a dual epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) inhibitor remains unproven in non-HER2-amplified metastatic breast cancer (MBC). EGF30008, a phase III trial of letrozole and lapatinib versus letrozole and placebo, demonstrated that lapatinib significantly improves outcome for postmenopausal women with HER2-amplified, but not HER2-negative, MBC. The hypothesis that low hormone receptor status is associated with benefit in this HER2-negative cohort was tested. EXPERIMENTAL DESIGN: A blinded retrospective biomarker evaluation used immunohistochemistry to semi-quantify estrogen receptor (ER) and progesterone receptor (PgR) expression (n=821/952). HER2 status was determined by immunohistochemistry and confirmed by fluorescence in situ hybridization (n=326). Effects of these biomarkers on progression-free survival (PFS) were examined in patients with available tissue. RESULTS: In HER2-negative, ER positive MBC, median PFS was analyzed by ER and PgR expression (H-score) by quartile (Q). There was significant improvement in patients with low ER expression (Q1, H-score <160) with lapatinib and letrozole (13.6 vs 6.7 months; P=0.01). No benefit was associated with stronger ER expression (Q2/3, H-score >=160 and <250; 13.6 vs 14.2 months; Q4, H-score >=250; 11.2 vs 14.2 months). There was no association between PgR H-score and benefit from lapatinib. CONCLUSIONS: In postmenopausal patients with advanced

hormone receptor-positive disease, weak ER expression is associated with worse outcome with letrozole treatment compared with the combination. Addition of lapatinib significantly improved PFS for this patient subgroup and augments data supporting interaction between steroid hormone and peptide hormone signaling. A prospective study validating this hypothesis is required.

[330]

**TÍTULO / TITLE:** - Absence of effect of SLC22A2 genotype on cisplatin-induced nephrotoxicity in oesophageal cancer patients receiving cisplatin and 5-fluorouracil: report of results discordant with those of earlier studies.

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

**REVISTA / JOURNAL:** - J Clin Pharm Ther. 2013 Sep 16. doi: 10.1111/jcpt.12097.

●● [Enlace al texto completo \(gratis o de pago\) 1111/jcpt.12097](#)

**AUTORES / AUTHORS:** - Hinai Y; Motoyama S; Nioka T; Miura M

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, Akita University Hospital, Akita, Japan.

**RESUMEN / SUMMARY:** - WHAT IS KNOWN AND OBJECTIVE: Cancer patients treated with cisplatin chemotherapy frequently experience drug-induced nephrotoxicity. Clinical studies using a single chemotherapeutic regimen or large sample sizes for patients with the SLC22A2 808T allele have not been reported. Here, we examined 95 patients with oesophageal cancer who received 5-fluorouracil and cisplatin (FP) to determine whether nephrotoxicity was affected by SLC22A2 808G>T polymorphism. METHODS: The change rate of the estimated glomerular filtration rate (eGFR) was used for the evaluation of cisplatin-induced nephrotoxicity and calculated for each patient according to the following formula: change rate = (prechemotherapy value - post-chemotherapy value)/prechemotherapy value. Genotyping of SLC22A2 808G>T was carried out using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. RESULTS: The eGFR after FP chemotherapy was significantly lower than that before chemotherapy, and the mean difference in eGFR was 25.7 mL/min (P < 0.01). There was no significant difference in the mean change rate of the eGFR following FP chemotherapy between the SLC22A2 808GG genotype (n = 70) and the 808GT+TT genotypes (n = 25) (27.9% and 27.8%, respectively). In multiple regression analyses, the change rate of eGFR following FP chemotherapy was associated with the eGFR value prior to chemotherapy (P = 0.04). WHAT IS NEW AND CONCLUSION: In FP chemotherapy for oesophageal cancers, cisplatin-induced nephrotoxicity seems to be unaffected by the SLC22A2 808G>T polymorphism. The eGFR prior to chemotherapy might be an important risk factor for cisplatin-induced nephrotoxicity. Our present study was estimated with a single chemotherapeutic regimen, eGFR, and was calculated using serum creatinine, age and the sex of the patient and sample sizes of 25 patients with SLC22A2 808T allele. However, further examinations with a larger sample size to corroborate the study results might be necessary.

[331]

**TÍTULO / TITLE:** - Induction of differential apoptotic pathways in multiple myeloma cells by class-selective histone deacetylase inhibitors.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Oct 22. doi: 10.1038/leu.2013.301.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.301](#)

**AUTORES / AUTHORS:** - Hideshima T; Mazitschek R; Santo L; Mimura N; Gorgun G; Richardson PG; Raje N; Anderson KC

**INSTITUCIÓN / INSTITUTION:** - Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA.

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[332]

**TÍTULO / TITLE:** - Impact of DNA methyltransferases on the epigenetic regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor expression in malignant melanoma.

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

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Nov 29;441(4):743-50. doi: 10.1016/j.bbrc.2013.10.114. Epub 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.10.114](#)

**AUTORES / AUTHORS:** - Venza M; Visalli M; Catalano T; Fortunato C; Oteri R; Teti D; Venza I

**INSTITUCIÓN / INSTITUTION:** - Department of Experimental Specialized Medical and Surgical and Odontostomatology Sciences, University of Messina, Messina, Italy.

**RESUMEN / SUMMARY:** - Aberrant promoter methylation and resultant silencing of TRAIL decoy receptors were reported in a variety of cancers, but to date little is known about the relevance of this epigenetic modification in melanoma. In this study, we examined the methylation and the expression status of TRAIL receptor genes in cutaneous and uveal melanoma cell lines and specimens and their interaction with DNA methyltransferases (DNMTs) DNMT1, DNMT3a, and DNMT3b. DR4 and DR5 methylation was not frequent in cutaneous melanoma but on the contrary it was very frequent in uveal melanoma. No correlation between methylation status of DR4 and DR5 and gene expression was found. DcR1 and DcR2 were hypermethylated with very high frequency in both cutaneous and uveal melanoma. The concordance between methylation and loss of gene expression ranged from 91% to 97%. Here we showed that DNMT1 was crucial for DcR2 hypermethylation and that DNMT1 and DNMT3a coregulate the methylation status of DcR1. Our work also revealed the critical relevance of DcR1 and DcR2 expression in cell growth and apoptosis either in cutaneous or uveal melanoma. In conclusion, the results presented here claim for a relevant impact of aberrant methylation of decoy receptors in melanoma and allow to understand how the silencing of DcR1 and DcR2 is related to melanomagenesis.

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[333]

**TÍTULO / TITLE:** - Tetraspanins CD9 and CD151, epidermal growth factor receptor and cyclooxygenase-2 expression predict malignant progression in oral epithelial dysplasia.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2864-74. doi: 10.1038/bjc.2013.600. Epub 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.600](#)

**AUTORES / AUTHORS:** - Nankivell P; Williams H; McConkey C; Webster K; High A; Maclennan K; Senguven B; Rabbitts P; Mehanna H

**INSTITUCIÓN / INSTITUTION:** - 1] Institute of Head and Neck Studies and Education (InHANSE), School of Cancer Sciences, University of Birmingham, Birmingham B15 2TT, UK [2] Department of Otolaryngology, University Hospital Coventry and Warwickshire, Coventry CV2 2DX, UK [3] Department of Otolaryngology, University Hospital Birmingham, Birmingham B15 2WB, UK.

**RESUMEN / SUMMARY:** - Background: Prognostic biomarkers aim to improve on the current inadequate method of histological assessment to identify patients with oral epithelial dysplasia at greatest risk of malignant transformation. We aimed to assess the prognostic ability of six protein biomarkers linked to the epidermal growth factor receptor (EGFR) pathway, including three tetraspanins, in a large multicentre oral dysplasia cohort. Methods: One hundred and forty-eight cases with varying degrees of epithelial dysplasia underwent immunohistochemical assessment for CD9, CD151, CD82, EGFR, Her-2, and COX-2. Scoring was performed independently by two observers. Univariate analyses using both logistic and Cox regression models and a multivariate regression were performed. Results: Malignant progression was significantly greater in those cases with decreased expression of CD9 (P=0.02), and increased expression of CD151 (P=0.02), EGFR (P=0.04), and COX-2 (P=0.003). Histological grade (P=0.0002) and morphology (P=0.03) were also prognostic, whereas smoking and alcohol were not. The optimal combination by backward-variable selection was of histological grade (hazard ratio (HR) 1.64; 95% CI 1.12, 2.40), COX-2 overexpression (HR 1.12; 1.02, 1.24) and CD9 underexpression (HR 0.88; 0.80, 0.97). CD82 and Her-2 demonstrated no prognostic ability. Conclusion: This is the first study of the expression and prognostic potential of the tetraspanins in oral dysplasia. A combination of certain biomarkers with clinical factors appeared to improve the accuracy of determining the risk of malignancy in individuals with oral dysplasia. These findings may also offer potential new therapeutic approaches for this condition.

[334]

**TÍTULO / TITLE:** - Aspirin-induced Bcl-2 translocation and its phosphorylation in the nucleus trigger apoptosis in breast cancer cells.

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

**REVISTA / JOURNAL:** - Exp Mol Med. 2013 Oct 11;45:e47. doi: 10.1038/emm.2013.91.

●● Enlace al texto completo (gratis o de pago) [1038/emm.2013.91](#)

**AUTORES / AUTHORS:** - Choi BH; Chakraborty G; Baek K; Yoon HS

**INSTITUCIÓN / INSTITUTION:** - 1] School of Biological Science, Nanyang Technological University, Singapore, Singapore [2] Pohang Center for Evaluation of Biomaterials, Pohang Technopark, Pohang, South Korea.

**RESUMEN / SUMMARY:** - Here, we report that B-cell lymphoma 2 (Bcl-2) is a novel target molecule of aspirin in breast cancer cells. Aspirin influenced the formation of a complex by Bcl-2 and FKBP38 and induced the nuclear translocation of Bcl-2 and its phosphorylation. These events inhibited cancer cell proliferation and subsequently enhanced MCF-7 breast cancer cell apoptosis. Bcl-2 knockdown using small interfering RNA (siRNA) delayed apoptotic cell death, which correlated with increased proliferation following aspirin exposure. In contrast, Bcl-2 overexpression enhanced the onset of aspirin-induced apoptosis, which was also associated with a significant increase in Bcl-

2 phosphorylation in the nucleus. Therefore, this study may provide novel insight into the molecular mechanism of aspirin, particularly its anticancer effects in Bcl-2- and estrogen receptor-positive breast cancer cells.

[335]

**TÍTULO / TITLE:** - Pharmacogenomics of Cantharidin in Tumor Cells.

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

**REVISTA / JOURNAL:** - Biochem Pharmacol. 2013 Nov 11. pii: S0006-2952(13)00709-0. doi: 10.1016/j.bcp.2013.10.025.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.10.025](#)

**AUTORES / AUTHORS:** - Kadioglu O; Kermani NS; Kelter G; Schumacher U; Fiebig HH; Greten HJ; Efferth T

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany.

**RESUMEN / SUMMARY:** - Cantharis vesicatoria (blister beetle) is used in Chinese medicine and has been categorized as highly toxic in the Chinese pharmacopeia. In Europe, Cantharis patches have been used since ages to treat various skin-related diseases. We investigated the cytotoxicity of the Cantharis ingredient, cantharidin, in 41 tumor cell lines (Oncotest panel) and compared the results with those of 60 cell lines of the National Cancer Institute, USA. We found profound activity at low micromolar concentrations (log<sub>10</sub>IC<sub>50</sub> values between -6.980 to -5.009M). Cantharidin bound to protein phosphatase 2A (PP2A) with higher affinity (-8.12kcal/mol) than to PP1 (-6.25kcal/mol) in molecular docking analyses. Using a PCR array for 84 apoptosis genes, cantharidin treatment upregulated gene expression of caspase-1 and nerve growth factor receptor, but downregulated mRNA expression of Bcl-2 like protein 10, Fas ligand, and tumor necrosis factor-alpha. By using COMPARE analysis of microarray-based transcriptome-wide mRNA expressions, 21 genes were found to significantly correlate with response of 60 tumor cell lines to cantharidin. As shown by hierarchical cluster analysis and chi-squared test, the distribution of cell lines in the dendrogram according to their gene expression profiles predicted sensitivity or resistance to cantharidin (P=6.482x10<sup>-5</sup>). The compassionate use of Cantharis patches in two patients suffering from basalioma and Mycosis fungoides, respectively, considerably improved the diseases without signs of toxicity. In conclusion, these results indicate that cantharidin may be a useful candidate to develop novel strategies for cancer therapy.

[336]

**TÍTULO / TITLE:** - Synergistic inhibition of lung cancer cell lines by (-)-epigallocatechin-3-gallate in combination with clinically used nitrocatechol inhibitors of catechol-O-methyltransferase.

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

**REVISTA / JOURNAL:** - Carcinogenesis. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt347](#)

**AUTORES / AUTHORS:** - Forester SC; Lambert JD

**INSTITUCIÓN / INSTITUTION:** - Center of Excellence for Plant and Mushroom Foods for Human Health, Department of Food Science.

**RESUMEN / SUMMARY:** - (-)-Epigallocatechin-3-gallate (EGCG) has exhibited been studied for lung cancer inhibitory activity in vitro and in animal models, but it is rapidly methylated and inactivated by catechol-O-methyltransferase (COMT). Entacapone and tolcapone, COMT inhibitors, are used to mitigate the symptoms of Parkinson's disease. We investigated the synergistic effects of entacapone/tolcapone and EGCG against lung cancer cell lines in culture. EGCG, entacapone and tolcapone inhibited the growth of H1299 human lung cancer cells (IC50 = 174.9, 76.8 and 29.3 microM, respectively) and CL-13 murine lung cancer cells (IC50 = 181.5, 50.7 and 19.7 microM, respectively) as single agents following treatment for 72h. Treatment with 1:10, 1:5, 1:2.5 and 1:1 combinations of EGCG and tolcapone or entacapone resulted in synergistically enhanced growth inhibition. The growth inhibitory effect of the combinations was mediated by induction of intracellular oxidative stress, cell cycle arrest and decreased nuclear translocation of nuclear factor-kappaBeta. Methylation of EGCG was dose dependently inhibited by entacapone and tolcapone (IC50 = 10 and 20 microM, respectively) in a cell-free system, and both compounds increased the intracellular levels of unmethylated EGCG. Treatment of mice with EGCG in combination with tolcapone increased the bioavailability of EGCG and decreased the methylation of plasma norepinephrine: no apparent liver or behavioral toxicity was observed. In conclusion, the combination of EGCG and entacapone/tolcapone synergistically inhibited the growth of lung cancer cells in culture, and the mechanistic basis for this synergy is likely due in part to inhibition of COMT with resultant increase in the levels of unmetabolized EGCG.

[337]

**TÍTULO / TITLE:** - Apolipoprotein C-II Is a Potential Serum Biomarker as a Prognostic Factor of Locally Advanced Cervical Cancer After Chemoradiation Therapy.

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

**REVISTA / JOURNAL:** - Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):1155-61. doi: 10.1016/j.ijrobp.2013.08.023. Epub 2013 Oct 10.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ijrobp.2013.08.023](#)

**AUTORES / AUTHORS:** - Harima Y; Ikeda K; Utsunomiya K; Komemushi A; Kanno S; Shiga T; Tanigawa N

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology, Takii Hospital, Kansai Medical University, Moriguchi, Osaka, Japan. Electronic address: [harima@takii.kmu.ac.jp](mailto:harima@takii.kmu.ac.jp).

**RESUMEN / SUMMARY:** - PURPOSE: To determine pretreatment serum protein levels for generally applicable measurement to predict chemoradiation treatment outcomes in patients with locally advanced squamous cell cervical carcinoma (CC). METHODS AND MATERIALS: In a screening study, measurements were conducted twice. At first, 6 serum samples from CC patients (3 with no evidence of disease [NED] and 3 with cancer-caused death [CD]) and 2 from healthy controls were tested. Next, 12 serum samples from different CC patients (8 NED, 4 CD) and 4 from healthy controls were examined. Subsequently, 28 different CC patients (18 NED, 10 CD) and 9 controls were analyzed in the validation study. Protein chips were treated with the sample sera, and the serum protein pattern was detected by surface-enhanced laser desorption and

ionization-time-of-flight mass spectrometry (SELDI-TOF MS). Then, single MS-based peptide mass fingerprinting (PMF) and tandem MS (MS/MS)-based peptide/protein identification methods, were used to identify protein corresponding to the detected peak. And then, turbidimetric assay was used to measure the levels of a protein that indicated the best match with this peptide peak. RESULTS: The same peak 8918 m/z was identified in both screening studies. Neither the screening study nor the validation study had significant differences in the appearance of this peak in the controls and NED. However, the intensity of the peak in CD was significantly lower than that of controls and NED in both pilot studies ( $P=.02$ ,  $P=.04$ ) and validation study ( $P=.01$ ,  $P=.001$ ). The protein indicated the best match with this peptide peak at 8918 m/z was identified as apolipoprotein C-II (ApoC-II) using PMF and MS/MS methods. Turbidimetric assay showed that the mean serum levels of ApoC-II tended to decrease in CD group when compared with NED group ( $P=.078$ ). CONCLUSION: ApoC-II could be used as a biomarker for detection in predicting and estimating the radiation treatment outcome of patients with CC.

[338]

**TÍTULO / TITLE:** - Pretreatment ADC Histogram Analysis Is a Predictive Imaging Biomarker for Bevacizumab Treatment but Not Chemotherapy in Recurrent Glioblastoma.

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

**REVISTA / JOURNAL:** - AJNR Am J Neuroradiol. 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [3174/ajnr.A3748](#)

**AUTORES / AUTHORS:** - Ellingson BM; Sahebjam S; Kim HJ; Pope WB; Harris RJ; Woodworth DC; Lai A; Nghiemphu PL; Mason WP; Cloughesy TF

**INSTITUCIÓN / INSTITUTION:** - Departments of Radiological Sciences, Biomedical Physics, Bioengineering, and Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; and Department of Medicine, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada.

**RESUMEN / SUMMARY:** - BACKGROUND AND PURPOSE:Pre-treatment ADC characteristics have been shown to predict response to bevacizumab in recurrent glioblastoma multiforme. However, no studies have examined whether ADC characteristics are specific to this particular treatment. The purpose of the current study was to determine whether ADC histogram analysis is a bevacizumab-specific or treatment-independent biomarker of treatment response in recurrent glioblastoma multiforme.MATERIALS AND METHODS:Eighty-nine bevacizumab-treated and 43 chemotherapy-treated recurrent glioblastoma multiformes never exposed to bevacizumab were included in this study. In all patients, ADC values in contrast-enhancing ROIs from MR imaging examinations performed at the time of recurrence, immediately before commencement of treatment for recurrence, were extracted and the resulting histogram was fitted to a mixed model with a double Gaussian distribution. Mean ADC in the lower Gaussian curve was used as the primary biomarker of interest. The Cox proportional hazards model and log-rank tests were used for survival analysis.RESULTS:Cox multivariate regression analysis accounting for the interaction between bevacizumab- and non-bevacizumab-treated patients suggested that the ability of the lower Gaussian curve to predict survival is dependent on treatment (progression-free survival,  $P = .045$ ; overall survival,  $P = .003$ ). Patients with

bevacizumab-treated recurrent glioblastoma multiforme with a pretreatment lower Gaussian curve > 1.2  $\mu\text{m}^2/\text{ms}$  had a significantly longer progression-free survival and overall survival compared with bevacizumab-treated patients with a lower Gaussian curve < 1.2  $\mu\text{m}^2/\text{ms}$ . No differences in progression-free survival or overall survival were observed in the chemotherapy-treated cohort. Bevacizumab-treated patients with a mean lower Gaussian curve > 1.2  $\mu\text{m}^2/\text{ms}$  had a significantly longer progression-free survival and overall survival compared with chemotherapy-treated patients. CONCLUSIONS: The mean lower Gaussian curve from ADC histogram analysis is a predictive imaging biomarker for bevacizumab-treated, not chemotherapy-treated, recurrent glioblastoma multiforme. Patients with recurrent glioblastoma multiforme with a mean lower Gaussian curve > 1.2  $\mu\text{m}^2/\text{ms}$  have a survival advantage when treated with bevacizumab.

[339]

**TÍTULO / TITLE:** - Poor responses to tyrosine kinase inhibitors in a child with precursor B-cell acute lymphoblastic leukemia with SNX2-ABL1 chimeric transcript.

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

**REVISTA / JOURNAL:** - Eur J Haematol. 2013 Nov 11. doi: 10.1111/ejh.12234.

●● Enlace al texto completo (gratis o de pago) [1111/ejh.12234](#)

**AUTORES / AUTHORS:** - Masuzawa A; Kiyotani C; Osumi T; Shioda Y; Iijima K; Tomita O; Nakabayashi K; Oboki K; Yasuda K; Sakamoto H; Ichikawa H; Hata K; Yoshida T; Matsumoto K; Kiyokawa N; Mori T

**INSTITUCIÓN / INSTITUTION:** - Division of Pediatric Oncology, National Center for Child Health and Development, Setagaya-ku, Japan.

**RESUMEN / SUMMARY:** - In addition to BCR, various rare fusion partners for the ABL1 gene have been reported in leukemia. We have identified the fusion gene SNX2-ABL1 in a pediatric case of acute lymphoblastic leukemia (ALL), which has only once previously been reported in an adult patient. Cytogenetic analysis detected this fusion gene arising from a t(5;9)(q22;q34) translocation. ALL cells carrying a SNX2-ABL1 fusion exhibited a BCR-ABL1+ ALL-like gene expression profile. The patient poorly responded to dasatinib but partially responded to imatinib. Treatment using tyrosine kinase inhibitors requires further investigation to optimize the genotype-based treatment stratification for patients with SNX2-ABL1 fusion.

[340]

**TÍTULO / TITLE:** - Quantitative assessment Ki-67 score for prediction of response to neoadjuvant chemotherapy in breast cancer.

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

**REVISTA / JOURNAL:** - Lab Invest. 2013 Nov 4. doi: 10.1038/labinvest.2013.128.

●● Enlace al texto completo (gratis o de pago) [1038/labinvest.2013.128](#)

**AUTORES / AUTHORS:** - Brown JR; Digiovanna MP; Killelea B; Lannin DR; Rimm DL

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Yale Pathology Tissue Services, Yale University Medical School, New Haven, CT, USA.

**RESUMEN / SUMMARY:** - Measurement of Ki-67, a marker of cell proliferation, has been associated with response to therapy, but methods of measurement are controversial. Here we use a quantitative objective measurement for Ki-67 to

determine the best method for assessment of Ki-67 for prediction of response to neoadjuvant chemotherapy. Analysis was conducted on a cohort of 105 consecutive invasive breast cancer patients that received neoadjuvant therapy between 2002 and 2010, and on whom pre-surgical biopsies were obtainable. Ki-67 expression was measured using quantitative immunofluorescence automated quantitative analysis (AQUA) technology. Images for each specimen were collected for 5 to 115 fields of view (FOVs) and summary scores were obtained, corresponding to the average and maximum of all the FOVs. AQUA scoring (using both intensity and area) was comparable to automated calculation of percentage of positive nuclei for prediction of response to chemotherapy (OR: 2.832 vs 2.712). Both the average and maximum AQUA score showed Ki-67 expression was directly correlated to pathological complete response (pCR; average P=0.0002; maximum P=0.0011). Although examining the maximum FOV was more predictive of response to therapy (OR: 3.546 vs 2.832), averaging all fields provided more sensitivity and specificity (AUC 0.769 vs 0.732). Ki-67 average (P=0.0025) and maximum (P=0.0239) AQUA score were also significant predictors of pCR in a multivariable analysis, including tumor size, nuclear grade, nodal status, ER status, and HER2 status. Measurement of Ki-67 expression by objective quantitative methods shows increased Ki-67 levels are an independent predictor of response to neoadjuvant chemotherapy. Laboratory Investigation advance online publication, 4 November 2013; doi:10.1038/labinvest.2013.128.

[341]

**TÍTULO / TITLE:** - MST1 activation by curcumin mediates JNK activation, Foxo3a nuclear translocation and apoptosis in melanoma cells.

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

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Nov 8;441(1):53-8. doi: 10.1016/j.bbrc.2013.10.008. Epub 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.10.008](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, Shandong Ji-ning No. 1 People's Hospital, Shandong Province 272011, PR China. Electronic address: [tengyu33@yahoo.com](mailto:tengyu33@yahoo.com).

**RESUMEN / SUMMARY:** - Different groups including ours have shown that curcumin induces melanoma cell apoptosis, here we focused the role of mammalian Sterile 20-like kinase 1 (MST1) in it. We observed that curcumin activated MST1-dependent apoptosis in cultured melanoma cells. MST1 silencing by RNA interference (RNAi) suppressed curcumin-induced cell apoptosis, while MST1 over-expressing increased curcumin sensitivity. Meanwhile, curcumin induced reactive oxygen species (ROS) production in melanoma cells, and the ROS scavenger, N-acetyl-cysteine (NAC), almost blocked MST1 activation to suggest that ROS might be required for MST1 activation by curcumin. c-Jun N-terminal protein kinase (JNK) activation by curcumin was dependent on MST1, since MST1 inhibition by RNAi or NAC largely inhibited curcumin-induced JNK activation. Further, curcumin induced Foxo3 nuclear translocation and Bim-1 (Foxo3 target gene) expression in melanoma cells, such an effect by curcumin was inhibited by MST1 RNAi. In conclusion, we suggested that MST1 activation by curcumin mediates JNK activation, Foxo3a nuclear translocation and apoptosis in melanoma cells.

[342]

**TÍTULO / TITLE:** - The cytotoxic effect of alpha-tomatine in MCF-7 human adenocarcinoma breast cancer cells depends on its interaction with cholesterol in incubation media and does not involve apoptosis induction.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2593-602. doi: 10.3892/or.2013.2778. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2778](#)

**AUTORES / AUTHORS:** - Sucha L; Hroch M; Rezacova M; Rudolf E; Havelek R; Sispara L; Cmielova J; Kohlerova R; Bezrouk A; Tomsik P

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Biochemistry, Charles University in Prague, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic.

**RESUMEN / SUMMARY:** - In recent years, alpha-tomatine has been studied for its anticancer activity. In the present study, we focused on the cytotoxic effect of alpha-tomatine in the MCF-7 human breast adenocarcinoma cell line, its mechanism of action, biotransformation and stability in the culture medium. We observed an inhibition of cell proliferation and viability at concentrations of 6 and 9 microM but then a recovery of cells occurred. The recovery was not caused by the biotransformation of alpha-tomatine in MCF-7 cells, but by a substantial decrease in the concentration of alpha-tomatine in the culture medium due to its binding with cholesterol. Regarding the mechanism of action of alpha-tomatine, we observed no DNA damage, no changes in the levels of the proteins p53 and p21(WAF1/Cip1), and no apoptosis (neither activated caspase-8 and -9, nor sub-G1 peak, or morphological signs). We found a loss of ATP in alpha-tomatine-treated cells. These results support the conclusion that alpha-tomatine does not induce apoptosis in the MCF-7 cell line.

[343]

**TÍTULO / TITLE:** - Phosphorylation of paxillin confers cisplatin resistance in non-small cell lung cancer via activating ERK-mediated Bcl-2 expression.

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

**REVISTA / JOURNAL:** - Oncogene. 2013 Oct 7. doi: 10.1038/onc.2013.389.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.389](#)

**AUTORES / AUTHORS:** - Wu DW; Wu TC; Wu JY; Cheng YW; Chen YC; Lee MC; Chen CY; Lee H

**INSTITUCIÓN / INSTITUTION:** - Graduate Institute of Cancer Biology and Drug Discovery, Taipei Medical University, Taipei, Taiwan, ROC.

**RESUMEN / SUMMARY:** - Paxillin (PXN) is required for receptor tyrosine kinase-mediated ERK activation, and the activation of the Raf/MEK/ERK cascade has been linked with Bcl-2 expression. We hypothesized that phosphorylation of PXN by the EGFR/Src pathway might contribute to cisplatin resistance via increased Bcl-2 expression. We show that cisplatin resistance was dependent on PXN expression, as evidenced by PXN overexpression in TL-13 and TL-10 cells and PXN knockdown in H23 and CL1-5 cells. Specific inhibitors of signaling pathways indicated that the phosphorylation of PXN at Y118 and Y31 via the Src pathway was responsible for cisplatin resistance. We further demonstrated that ERK activation was also dependent

on this PXN phosphorylation. Bcl-2 transcription was upregulated by phosphorylated PXN-mediated ERK activation via increased binding of phosphorylated CREB to the Bcl-2 promoter. A subsequent increase in Bcl-2 levels by a PXN/ERK axis was responsible for the resistance to cisplatin. Animal models further confirmed the findings of in vitro cells indicating that xenograft tumors induced by TL-13-overexpressing cells were successfully suppressed by cisplatin combined with Src or ERK inhibitor compared with treatment of cisplatin, Src inhibitor or ERK inhibitor alone. A positive correlation of phosphorylated PXN with phosphorylated ERK and Bcl-2 was observed in lung tumors from NSCLC patients. Patients with tumors positive for PXN, phosphorylated PXN, phosphorylated ERK and Bcl-2 more commonly showed a poorer response to cisplatin-based chemotherapy than did patients with negative tumors. Collectively, PXN phosphorylation might contribute to cisplatin resistance via activating ERK-mediated Bcl-2 transcription. Therefore, we suggest that Src or ERK inhibitor might be helpful to improve the sensitivity for cisplatin-based chemotherapy in NSCLC patients with PXN-positive tumors. Oncogene advance online publication, 7 October 2013; doi:10.1038/onc.2013.389.

[344]

**TÍTULO / TITLE:** - Carboplatin synergistically triggers the efficacy of photodynamic therapy via caspase 3-, 8-, and 12-dependent pathways in human anaplastic thyroid cancer cells.

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

**REVISTA / JOURNAL:** - Lasers Med Sci. 2013 Oct 10.

●● Enlace al texto completo (gratis o de pago) [1007/s10103-013-1452-9](#)

**AUTORES / AUTHORS:** - Biswas R; Chung PS; Moon JH; Lee SH; Ahn JC

**INSTITUCIÓN / INSTITUTION:** - Beckman Laser Institute Korea, Dankook University, 29-1, Anseo-dong, Cheonan, Chungnam, Republic of Korea, 330-714.

**RESUMEN / SUMMARY:** - Anaplastic thyroid cancer is one of the most aggressive forms of malignancies which grow very rapidly. Several conventional methods have been applied for the treatment of anaplastic thyroid cancer, but most of them were not successful in complete recovery of the patients. Therefore, a combination of two or more conventional modalities is being applied nowadays for the treatment of this type of cancer. In this present study, the combination of photodynamic therapy (PDT) and chemotherapy has been studied in anaplastic thyroid cancer. Human anaplastic thyroid cancer cells FRO were treated with a chemotherapy drug, carboplatin (cis-diammine-1,1-cyclobutanedicarboxyl-ateplatinum II (CBDCA)), and radachlorin-mediated PDT individually and in combination. Several parameters like cytotoxicity assay by MTT, apoptosis study by annexin V and propidium iodide, cell cycle analysis by flow cytometry, confocal microscopic study, and Western blot analysis for different apoptosis-related proteins like Bax, cytochrome c, caspases 3, 9, 8, and 12, etc. were studied to check the efficacy of the combination treatment as well as to find out the mechanism of this enhanced efficacy. Results showed that both PDT and CBDCA can induce apoptosis in FRO cells. However, a synergistic efficacy was observed when the cells were treated with CBDCA and PDT in combination. Changes in mitochondrial membrane potential and an increase in reactive oxygen species generation were observed in combination treatments. The enhanced expression of different apoptotic pathway-related proteins like Bax, cytochrome c, caspase 3, caspase 8, caspase 12,

etc. also confirmed the higher efficacy of combination treatment. Therefore, with this combination treatment, not only a higher efficacy can be achieved but also the effective dose of the chemotherapy drug can be reduced, and hence, the adverse side effects of the chemotherapy drugs can also be controlled.

[345]

**TÍTULO / TITLE:** - A novel binuclear palladacycle complex inhibits melanoma growth in vitro and in vivo through apoptosis and autophagy.

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

**REVISTA / JOURNAL:** - Biochem Pharmacol. 2013 Dec 15;86(12):1650-63. doi: 10.1016/j.bcp.2013.09.020. Epub 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.09.020](#)

**AUTORES / AUTHORS:** - Aliwaini S; Swarts AJ; Blanckenberg A; Mapolie S; Prince S

**INSTITUCIÓN / INSTITUTION:** - Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Observatory, 7925 Cape Town, South Africa. Electronic address: [saib.iwini@gmail.com](mailto:saib.iwini@gmail.com).

**RESUMEN / SUMMARY:** - Malignant melanoma is an aggressive skin cancer and it is reported to be the most treatment-resistant human cancer. Here we describe the anti-tumour activity of a novel binuclear palladacycle complex (AJ-5) in vertical growth phase (ME1402) and metastatic (WM1158) melanoma cell lines. We show that compared to normal control cell lines, AJ-5 is more effective in inhibiting the proliferation of ME1402 and WM1158 melanoma cells with IC50 values of 0.19 and 0.20 μM, respectively. Flow cytometry analyses showed that AJ-5 induced apoptosis (sub-G1 peak) which was confirmed by Annexin V-FITC/propidium iodide double-staining, nuclear fragmentation and an increase in the levels of PARP cleavage. Furthermore, AJ-5 was shown to induce both intrinsic and extrinsic apoptotic pathways as measured by PUMA, Bax and active caspases. Interestingly, AJ-5 treatment also simultaneously induced the formation of autophagosomes and led to an increase in the autophagy markers LC3II and Beclin1. Inhibition of autophagy reduced AJ-5 cytotoxicity suggesting that AJ-5 induced autophagy was a cell death and not cell survival mechanism. Moreover we show that AJ-5 induces the ATM-CHK2 DNA damage pathway and that its anti-tumour function is mediated by the p38 and ERK1/2 signalling pathways. Importantly, AJ-5 treatment efficiently reduced tumour growth in melanoma bearing mice and induced high levels of autophagy and apoptosis markers. Together these findings suggest that AJ-5 may be an effective chemotherapeutic drug in the treatment of melanoma, a highly aggressive and intractable cancer.

[346]

**TÍTULO / TITLE:** - High ubiquitous mitochondrial creatine kinase expression in hepatocellular carcinoma denotes a poor prognosis with highly malignant potential.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 15. doi: 10.1002/ijc.28547.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28547](#)

**AUTORES / AUTHORS:** - Uranbileg B; Enooku K; Soroida Y; Ohkawa R; Kudo Y; Nakagawa H; Tateishi R; Yoshida H; Shinzawa S; Moriya K; Ohtomo N; Nishikawa T; Inoue Y; Tomiya T; Kojima S; Matsuura T; Koike K; Yatomi Y; Ikeda H

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Laboratory Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

**RESUMEN / SUMMARY:** - We previously reported the increased serum mitochondrial creatine kinase (MtCK) activity in patients with hepatocellular carcinoma (HCC), mostly due to the increase in ubiquitous MtCK (uMtCK), and high uMtCK mRNA expression in HCC cell lines. We explored the mechanism(s) and the relevance of high uMtCK expression in HCC. In hepatitis C virus core gene transgenic mice, known to lose mitochondrial integrity in liver and subsequently develop HCC, uMtCK mRNA and protein levels were increased in HCC tissues but not in non-tumorous liver tissues. Transient overexpression of ankyrin repeat and suppressor of cytokine signaling box protein 9 (ASB9) reduced uMtCK protein levels in HCC cells, suggesting that increased uMtCK levels in HCC cells may be caused by increased gene expression and decreased protein degradation due to reduced ASB9 expression. The reduction of uMtCK expression by siRNA led to increased cell death, and reduced proliferation, migration and invasion in HCC cell lines. Then, consecutive 105 HCC patients, who underwent radiofrequency ablation with curative intent, were enrolled to analyze their prognosis. The patients with serum MtCK activity >19.4 U/L prior to the treatment had significantly shorter survival time than those with serum MtCK activity ≤19.4 U/L, where higher serum MtCK activity was retained as an independent risk for HCC-related death on multivariate analysis. In conclusion, high uMtCK expression in HCC may be caused by hepatocarcinogenesis per se but not by loss of mitochondrial integrity, of which ASB9 could be a negative regulator, and associated with highly malignant potential to suggest a poor prognosis. © 2013 UICC.

[347]

**TÍTULO / TITLE:** - Overexpression of the polarity protein PAR-3 in clear cell renal cell carcinoma is associated with poor prognosis.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 17. doi: 10.1002/ijc.28548.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ijc.28548](#)

**AUTORES / AUTHORS:** - Dugay F; Goff XL; Rioux-Leclercq N; Chesnel F; Jouan F; Henry C; Cabillic F; Verhoest G; Vigneau C; Arlot-Bonnemains Y; Belaud-Rotureau MA

**INSTITUCIÓN / INSTITUTION:** - CNRS - UMR 6290 (IGDR), Rennes 1 University - BIOSIT, 2 Ave du Pr L Bernard, 35042, Rennes, France; Cytogenetic and Cellular Biology Laboratory, CHU, Pontchaillou, 35043, Rennes, France.

**RESUMEN / SUMMARY:** - The partition-defective 3 (PAR-3) protein is implicated in the development and maintenance of cell polarity and is associated with proteins that mediate the changes in cytoskeleton organization required for cell polarity establishment. In this work, we used two original primary cell lines (R-180 and R-305) derived from clear cell Renal Cell Carcinoma (ccRCC) surgical specimens of a patient with unfavorable clinical course (R-180 cells) and a patient with favorable prognosis (R-305 cells) to identify genetic and molecular features that may explain the survival difference of the two patients. The cytogenetic analysis of these cell lines revealed that the PARD3 gene was amplified only in the R-180 cell line that was derived from an aggressive ccRCC. PARD3 gene amplification was associated with overexpression of the encoded protein and altered cytoskeleton organization. Consistently, PARD3 knockdown in R-180 cells restored the cytoskeleton organization and reduced cell

migration in comparison to non-transfected cells. Immunohistochemical analysis of ccRCC samples from a cohort of 96 patients with a follow-up of 6 years revealed that PAR-3 overexpression was correlated with poor survival. Our results suggest that PAR-3 has a role in the clinical aggressiveness of ccRCC, possibly by promoting cell migration. © 2013 Wiley Periodicals, Inc.

[348]

**TÍTULO / TITLE:** - Lipid raft-regulated IGF-1R activation antagonizes TRAIL-induced apoptosis in gastric cancer cells.

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

**REVISTA / JOURNAL:** - FEBS Lett. 2013 Nov 29;587(23):3815-23. doi: 10.1016/j.febslet.2013.10.007. Epub 2013 Oct 22.

●● Enlace al texto completo (gratis o de pago) [1016/j.febslet.2013.10.007](#)

**AUTORES / AUTHORS:** - Xu L; Qu X; Hu X; Zhu Z; Li C; Li E; Ma Y; Song N; Liu Y

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The First Hospital of China Medical University, Shenyang 110001, China.

**RESUMEN / SUMMARY:** - Gastric cancer cells are resistant to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and the resistance mechanism is not fully understood. In human gastric cancer MGC803 and BGC823 cells, TRAIL induces insulin-like growth factor-1 receptor (IGF-1R) pathway activation. Treatment with IGF-1R inhibitor OSI-906 or small interfering RNAs against IGF-1R, prevents IGF-1R pathway activation and increases TRAIL-induced apoptosis. The TRAIL-induced IGF-1R pathway activation is promoted by IGF-1R translocation into lipid rafts. Moreover, the translocation of IGF-1R into lipid rafts is regulated by Casitas B-lineage lymphoma b (Cbl-b). Taken together, TRAIL-induced IGF-1R activation antagonizes TRAIL-induced apoptosis by Cbl-b-regulated distribution of IGF-1R in lipid rafts.

[349]

**TÍTULO / TITLE:** - Effective down-regulation of signal transducer and activator of transcription 3 (STAT3) by polyplexes of siRNA and lipid-substituted polyethyleneimine for sensitization of breast tumor cells to conventional chemotherapy.

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

**REVISTA / JOURNAL:** - J Biomed Mater Res A. 2013 Oct 10. doi: 10.1002/jbma.34992.

●● Enlace al texto completo (gratis o de pago) [1002/jbma.34992](#)

**AUTORES / AUTHORS:** - Falamarzian A; Aliabadi HM; Molavi O; Seubert JM; Lai R; Uludag H; Lavasanifar A

**INSTITUCIÓN / INSTITUTION:** - Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada, T6G 2E1.

**RESUMEN / SUMMARY:** - Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that plays a major role in the development of resistance to conventional anti-cancer drugs in many types of cancer, when constitutively activated. Inhibition of STAT3 is considered as a promising strategy for inhibition of tumor growth and overcoming the drug resistance manifested. In this study, the capability of STAT3 knockdown by lipid substituted low molecular weight (2 kDa) polyethyleneimine (PEI2) complexes of STAT3-siRNA was assessed. The efficiency of PEI/STAT3-siRNA polyplexes in the induction of STAT3 associated cell death in wild type and drug-

resistant MDA-MB-435 breast cancer cells as mono-therapy and upon combination with chemotherapeutic agents, doxorubicin and paclitaxel, was also investigated. Our results identified linoleic acid-substituted (PEI-LA) polymer as the most efficient carrier among different lipid substituted PEI2 for siRNA delivery, leading to most STAT3 associated loss of cell viability in MDA-MB-435 cells. STAT3-siRNA delivery by the PEI-LA polymer resulted in efficient down-regulation of STAT3 at both mRNA and protein levels. Furthermore, pre-treatment of cancer cells with STAT3-siRNA formulation increased the cytotoxic effect of doxorubicin and paclitaxel in both wild type and drug resistant MDA-MB-435 cells. The results of this study point to the potential of PEI-LA polyplexes of STAT3-siRNA as inhibitors of STAT3 expression in breast tumor cells. The results also demonstrate an improved efficacy for chemotherapeutic drugs in combination with lipid-substituted low molecular weight PEI-LA/STAT3-siRNA complexes in comparison to drug therapy alone.

[350]

**TÍTULO / TITLE:** - Effective down-regulation of signal transducer and activator of transcription 3 (STAT3) by polyplexes of siRNA and lipid-substituted polyethyleneimine for sensitization of breast tumor cells to conventional chemotherapy.

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

**REVISTA / JOURNAL:** - J Biomed Mater Res A. 2013 Oct 25. doi: 10.1002/jbm.a.34992.

●● Enlace al texto completo (gratis o de pago) [1002/jbm.a.34992](#)

**AUTORES / AUTHORS:** - Falamarzian A; Montazeri Aliabadi H; Molavi O; Seubert JM; Lai R; Uludag H; Lavasanifar A

**INSTITUCIÓN / INSTITUTION:** - Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2E1.

**RESUMEN / SUMMARY:** - Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that plays a major role in the development of resistance to conventional anti-cancer drugs in many types of cancer, when constitutively activated. Inhibition of STAT3 is considered as a promising strategy for inhibition of tumor growth and overcoming the drug resistance manifested. In this study, the capability of STAT3 knockdown by lipid substituted low molecular weight (2 kDa) polyethyleneimine (PEI2) complexes of STAT3-siRNA was assessed. The efficiency of PEI/STAT3-siRNA polyplexes in the induction of STAT3 associated cell death in wild type and drug-resistant MDA-MB-435 breast cancer cells as monotherapy and upon combination with chemotherapeutic agents, doxorubicin and paclitaxel, was also investigated. Our results identified linoleic acid-substituted (PEI-LA) polymer as the most efficient carrier among different lipid substituted PEI2 for siRNA delivery, leading to most STAT3 associated loss of cell viability in MDA-MB-435 cells. STAT3-siRNA delivery by the PEI-LA polymer resulted in efficient down-regulation of STAT3 at both mRNA and protein levels. Furthermore, pre-treatment of cancer cells with STAT3-siRNA formulation increased the cytotoxic effect of doxorubicin and paclitaxel in both wild type and drug resistant MDA-MB-435 cells. The results of this study point to the potential of PEI-LA polyplexes of STAT3-siRNA as inhibitors of STAT3 expression in breast tumor cells. The results also demonstrate an improved efficacy for chemotherapeutic drugs in combination with lipid-substituted low molecular weight PEI-LA/STAT3-siRNA

complexes in comparison to drug therapy alone. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part A, 2013.

[351]

**TÍTULO / TITLE:** - Chemoradiation for anaplastic oligodendrogliomas: clinical outcomes and prognostic value of molecular markers.

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

**REVISTA / JOURNAL:** - J Neurooncol. 2013 Oct 26.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11060-013-1288-y](#)

**AUTORES / AUTHORS:** - Minniti G; Arcella A; Scaringi C; Lanzetta G; Di Stefano D; Scarpino S; Pace A; Giangaspero F; Osti MF; Enrici RM

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Sant'Andrea Hospital, University Sapienza, Via di Grottarossa 1035, 00189, Rome, Italy, [gminniti@ospedalesantandrea.it](mailto:gminniti@ospedalesantandrea.it).

**RESUMEN / SUMMARY:** - Combination of procarbazine, lomustine and vincristine (PCV) with radiation therapy (RT) has been associated with longer survival in patients with anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA), especially in those with chromosome 1p/19q codeletion. We report a multicenter retrospective study of 84 consecutive adult patients with AO and AOA treated with RT plus concomitant and adjuvant temozolomide (TMZ) between February 2004 and January 2011. Correlations between chromosome 1p/19q codeletion, isocitrate dehydrogenase1 (IDH1) mutation, and O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation with survival outcomes have been analyzed. For all 84 patients the median overall survival (OS) and progression-free survival rates were 55.6 and 45.2 months, respectively. Grade 3 or 4 hematological toxicity occurred in 17 % of patients. Chromosome 1p/19q codeletion was detected in 57 %, IDH1 mutation in 63 %, and MGMT promoter methylation in 74 % of evaluable patients. In multivariate analysis the presence of chromosome 1p/19q codeletion was associated with significant survival benefit (median OS 34 months in noncodeleted tumors and not reached in codeleted tumors; HR 0.16, 95 % CI 0.03-0.45; P = 0.005). IDH1 mutation was also of prognostic significance for longer survival (P = 0.001; HR 0.20, 95 % 0.06-0.41), whereas MGMT promoter methylation was only of borderline significance. The study indicates that RT with concomitant and adjuvant TMZ is a relatively safe treatment associated with longer survival in patients with 1p/19q codeleted and IDH1 mutated tumors. Results from ongoing randomized studies will be essential to clarify if RT plus TMZ may provide survival as good as or better than RT combined with PCV for patients with AO and AOA.

[352]

**TÍTULO / TITLE:** - Synergistic interaction of novel lactate dehydrogenase inhibitors with gemcitabine against pancreatic cancer cells in hypoxia.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 31. doi: 10.1038/bjc.2013.681.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.681](#)

**AUTORES / AUTHORS:** - Maftouh M; Avan A; Sciarrillo R; Granchi C; Leon LG; Rani R; Funel N; Smid K; Honeywell R; Boggi U; Minutolo F; Peters GJ; Giovannetti E

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, VU University Medical Center, De Boelelaan 1117, 1081HV, Amsterdam, Netherlands.

**RESUMEN / SUMMARY:** - Background:Hypoxia is a driving force in pancreatic-ductal-adenocarcinoma (PDAC) growth, metastasis and chemoresistance. The muscle-isoform of lactate dehydrogenase (LDH-A) constitutes a major checkpoint for the switch to anaerobic glycolysis, ensuring supply of energy and anabolites in hypoxic-environments. Therefore, we investigated the molecular mechanisms underlying the pharmacological interaction of novel LDH-A inhibitors in combination with gemcitabine in PDAC cells.Methods:Lactate dehydrogenase A levels were studied by quantitative RT-PCR, western blot, immunofluorescence and activity assays in 14 PDAC cells, including primary-cell-cultures and spheroids, in normoxic and hypoxic conditions. Cell proliferation, migration and key determinants of drug activity were evaluated by sulforhodamine-B-assay, wound-healing assay, PCR and LC-MS/MS.Results:Lactate dehydrogenase A was significantly increased under hypoxic conditions (1% O<sub>2</sub>), where the novel LDH-A inhibitors proved to be particularly effective (e.g., with IC<sub>50</sub> values of 0.9 vs 16.3 μM for NHI-1 in LPC006 in hypoxia vs normoxia, respectively). These compounds induced apoptosis, affected invasiveness and spheroid-growth, reducing expression of metalloproteinases and cancer-stem-like-cells markers (CD133+). Their synergistic interaction with gemcitabine, with combination index values <0.4 in hypoxia, might also be attributed to modulation of gemcitabine metabolism, overcoming the reduced synthesis of phosphorylated metabolites.Conclusion:Lactate dehydrogenase A is a viable target in PDAC, and novel LDH-A inhibitors display synergistic cytotoxic activity with gemcitabine, offering an innovative tool in hypoxic tumours.British Journal of Cancer advance online publication, 31 October 2013; doi:10.1038/bjc.2013.681 [www.bjcancer.com](http://www.bjcancer.com).

[353]

**TÍTULO / TITLE:** - Improving results of autologous stem cell transplantation for Philadelphia-positive acute lymphoblastic leukaemia in the era of tyrosine kinase inhibitors: A report from the Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation.

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

**REVISTA / JOURNAL:** - Eur J Cancer. 2013 Nov 5. pii: S0959-8049(13)00909-X. doi: 10.1016/j.ejca.2013.08.027.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.08.027](http://1016/j.ejca.2013.08.027)

**AUTORES / AUTHORS:** - Giebel S; Labopin M; Gorin NC; Caillot D; Leguay T; Schaap N; Michallet M; Dombret H; Mohty M

**INSTITUCIÓN / INSTITUTION:** - Dept. of Bone Marrow Transplantation and Onco-Hematology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Gliwice, Poland. Electronic address: [sgiebel@io.gliwice.pl](mailto:sgiebel@io.gliwice.pl).

**RESUMEN / SUMMARY:** - BACKGROUND: Outcome of Philadelphia-positive acute lymphoblastic leukaemia (Ph+ ALL) improved significantly with the introduction of tyrosine kinase inhibitors (TKIs). Autologous stem cell transplantation (ASCT) has never been considered a standard of care in this setting. The aim of our study was to analyse if results of ASCT improved in the era of TKIs. PATIENTS AND METHODS: One-hundred and seventy-seven adults with Ph+ ALL treated with ASCT in first complete remission were analysed for the impact of year of transplantation on

outcome. Additional analysis was performed including 32 patients for whom detailed data on the use of TKIs and the status of minimal residual disease were collected. RESULTS: The probability of the overall survival (OS) at 3years increased from 16% for transplants performed between 1996 and 2001 to 48% between 2002 and 2006 and 57% between 2007 and 2010 (P<.0001). Leukaemia-free survival (LFS) was 11%, 39% and 52%, respectively (P<.0001). Relapse incidence decreased from 70% to 45% and 45% (P=.01), respectively, while non-relapse mortality was 19%, 15% and 3% (P=.08). In a multivariate analysis, year of ASCT was the only independent factor influencing the risk of treatment failure (hazard ratio (HR)=0.37; P<.001). In a subgroup of 22 patients actually treated with TKIs and being in complete molecular remission at the time of ASCT, the LFS rate at 3years was 65%. CONCLUSIONS: Results of ASCT for Ph+ ALL improved significantly over time. Prospective, innovative studies are needed to verify the role of ASCT in this patient setting.

[354]

**TÍTULO / TITLE:** - Changes in plasma vascular endothelial growth factor at 8 weeks after sorafenib administration as predictors of survival for advanced hepatocellular carcinoma.

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

**REVISTA / JOURNAL:** - Cancer. 2013 Oct 7. doi: 10.1002/cncr.28384.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28384](#)

**AUTORES / AUTHORS:** - Tsuchiya K; Asahina Y; Matsuda S; Muraoka M; Nakata T; Suzuki Y; Tamaki N; Yasui Y; Suzuki S; Hosokawa T; Nishimura T; Ueda K; Kuzuya T; Nakanishi H; Itakura J; Takahashi Y; Kurosaki M; Enomoto N; Izumi N

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: A new predictive biomarker for determining prognosis in patients with hepatocellular carcinoma (HCC) who receive sorafenib is required, because achieving a reduction in tumor size with sorafenib is rare, even in patients who have a favorable prognosis. Vascular endothelial growth factor (VEGF) receptor is a sorafenib target. In the current study, the authors examined changes in plasma VEGF concentrations during sorafenib treatment and determined the clinical significance of VEGF as a prognostic indicator in patients with HCC. METHODS: Plasma VEGF concentrations were serially measured in 63 patients with advanced HCC before and during sorafenib treatment. A plasma VEGF concentration that decreased >5% from the pretreatment level at 8 weeks was defined as a "VEGF decrease." An objective tumor response was determined using modified Response Evaluation Criteria in Solid Tumors 1 month after the initiation of therapy and every 3 months thereafter. RESULTS: Patients who had a VEGF decrease at week 8 (n = 14) had a longer median survival than those who did not have a VEGF decrease (n = 49; 30.9 months vs 14.4 months; P = .038). All patients who had a VEGF decrease survived for >6 months, and the patients who had both a VEGF decrease and an alpha-fetoprotein response (n = 6) survived during the observation period (median, 19.7 months; range, 6.5-31.0 months). In univariate analyses, a VEGF decrease, radiologic findings classified as progressive disease, and major vascular invasion were associated significantly with 1-year survival; and, in multivariate analysis, a VEGF decrease was identified as an independent factor associated significantly with survival.

CONCLUSIONS: A plasma VEGF concentration decrease at 8 weeks after starting sorafenib treatment may predict favorable overall survival in patients with advanced HCC. Cancer 2013. © 2013 American Cancer Society.

[355]

**TÍTULO / TITLE:** - Aurora kinase A (AURKA) expression in colorectal cancer liver metastasis is associated with poor prognosis.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 29;109(9):2445-52. doi: 10.1038/bjc.2013.608. Epub 2013 Oct 8.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.608](#)

**AUTORES / AUTHORS:** - Goos JA; Coupe VM; Diosdado B; Delis-Van Diemen PM; Karga C; Belien JA; Carvalho B; van den Tol MP; Verheul HM; Geldof AA; Meijer GA; Hoekstra OS; Fijneman RJ

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Pathology, VU University Medical Center, De Boelelaan 1117, Amsterdam HV 1081, The Netherlands [2] Department of Radiology and Nuclear Medicine, VU University Medical Center, De Boelelaan 1117, Amsterdam HV 1081, The Netherlands.

**RESUMEN / SUMMARY:** - Background:Five-year survival after resection of colorectal cancer liver metastasis (CRCLM) is <30%. We recently found that aurora kinase A (AURKA) drives 20q gain-associated tumour progression and is associated with disease recurrence. This study evaluates the prognostic value of AURKA expression in CRCLM of patients who underwent liver resection.Methods:Tissue microarrays (TMAs) were generated using formalin-fixed paraffin-embedded CRCLM and matched primary tumour from a multi-institutional cohort of patients with CRCLM who underwent liver resection between 1990 and 2010. Tissue microarrays were stained for AURKA using immunohistochemistry, and a hazard rate ratio (HRR) for the association between overall survival (OS) and nuclear AURKA expression in CRCLM was calculated. Results were validated by 500-fold cross-validation.Results:The expression of AURKA was evaluated in CRCLM of 343 patients. High AURKA expression was associated with poor OS (HRR 1.55, P<0.01), with a cross-validated average HRR of 1.57 (P=0.02). Average HRR was adjusted for the established prognostic clinicopathological variables in a multivariate analysis (average HRR 1.66; P=0.02). The expression of AURKA in CRCLM was correlated to its expression in corresponding primary tumour (P<0.01).Conclusion:The expression of AURKA protein is a molecular biomarker with prognostic value for patients with CRCLM, independent of established clinicopathological variables.

[356]

**TÍTULO / TITLE:** - A luteinizing hormone-releasing hormone agonist plus an aromatase inhibitor as second-line endocrine therapy in premenopausal females with hormone receptor-positive metastatic breast cancer.

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

**REVISTA / JOURNAL:** - Surg Today. 2013 Nov 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00595-013-0765-4](#)

**AUTORES / AUTHORS:** - Tanaka K; Tokunaga E; Yamashita N; Taketani K; Akiyoshi S; Morita M; Maehara Y

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 811-1395, Japan, [ktanaka@surg2.med.kyushu-u.ac.jp](mailto:ktanaka@surg2.med.kyushu-u.ac.jp).

**RESUMEN / SUMMARY:** - **PURPOSE:** The aim of the current study was to explore the efficacy and safety of combination therapy using a luteinizing hormone-releasing hormone (LHRH) agonist plus an aromatase inhibitor (AI) as second-line therapy in premenopausal females with hormone receptor (HR)-positive recurrent or metastatic breast cancer (MBC). **METHODS:** A retrospective analysis was conducted in patients registered in the breast cancer database of our institution between January 2001 and December 2012. The breast cancer database identified 14 premenopausal patients who had been treated with an LHRH agonist plus AI for HR-positive recurrent or MBC. **RESULTS:** Fourteen patients with recurrent breast cancer (N = 10) or metastatic disease at primary diagnosis (N = 4) were included in the present study. All patients had previously been treated with an LHRH agonist plus tamoxifen. The clinical benefit rate was 71.4 % and the median TTP was 11 months (95 % confidence interval 1.7-20.3 months). One patient discontinued treatment because of liver dysfunction (grade 3). **CONCLUSIONS:** The combination of an LHRH agonist plus an AI is a treatment option for premenopausal females with HR-positive MBC that can prolong the chemotherapy-free interval and yield effective disease stabilization.

[357]

**TÍTULO / TITLE:** - Role of anti-apoptotic pathways activated by BCR/ABL in the resistance of chronic myeloid leukemia cells to tyrosine kinase inhibitors.

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

**REVISTA / JOURNAL:** - Acta Biochim Pol. 2013 Nov 22.

**AUTORES / AUTHORS:** - Danisz K; Blasiak J

**INSTITUCIÓN / INSTITUTION:** - Faculty of Biology and Environmental Protection, Department of Molecular Genetics, University of Lodz, Lodz, Poland.

**RESUMEN / SUMMARY:** - Chronic myeloid leukemia (CML) is a hematological stem cell disorder characterized by the excessive proliferation of the myeloid lineage. In its initial chronic phase, the myeloid progenitor cells expand and demonstrate apparently normal differentiation. The disease may then transform into the accelerated phase, usually associated with resistance to therapy, and finally, into acute leukemic progression phase - blast crisis. Abnormal myeloid cells produce progenitors, which have lost their ability to differentiate, but retain the capacity to proliferate. The molecular hallmark of CML is the Philadelphia chromosome, resulting from reciprocal chromosome translocation, t(9;22)(q34;q11), and containing the BCR/ABL fusion gene, producing the BCR/ABL protein with a constitutive tyrosine kinase activity. BCR/ABL-positive cells have faster growth and proliferation over their normal counterparts and are resistant to apoptosis. Introduction of imatinib (IM), a tyrosine kinase inhibitor, revolutionized the therapy of CML, changing it from a fatal disease into a chronic disorder. However, some patients show a primary resistance to IM, others acquire such resistance in the course of therapy. Therefore, a small number of leukemic stem cells retains self-renewal capacity under IM treatment. Because BCR/ABL is involved in many signaling pathways, some of them may be essential for resistance to IM-induced apoptosis. The

PI3K/AKT, Ras and JAK/STAT signaling pathways are involved in resistance to apoptosis and can be activated by BCR/ABL. Therefore, they can be candidates for BCR/ABL-dependent pro-survival pathway(s), allowing a fraction of CML cells to withstand treatment with tyrosine kinase inhibitors.

[358]

**TÍTULO / TITLE:** - Expression of SSTR2a, but not of SSTRs 1, 3, or 5 in Somatotroph Adenomas Assessed by Monoclonal Antibodies Was Reduced by Octreotide and Correlated With the Acute and Long-Term Effects of Octreotide.

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

**REVISTA / JOURNAL:** - J Clin Endocrinol Metab. 2013 Nov;98(11):E1730-9. doi: 10.1210/jc.2013-2145. Epub 2013 Oct 3.

●● [Enlace al texto completo \(gratis o de pago\) 1210/jc.2013-2145](#)

**AUTORES / AUTHORS:** - Casar-Borota O; Heck A; Schulz S; Nesland JM; Ramm-Petersen J; Lekva T; Alafuzoff I; Bollerslev J

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**RESUMEN / SUMMARY:** - Context: Reduced expression of somatostatin receptors (SSTRs) in somatotroph adenomas and their potential down-regulation after medical treatment may explain the unsatisfactory response to octreotide in particular acromegalic patients. The expression of SSTRs other than SSTR2a has not been studied in large, unselected cohorts using novel rabbit monoclonal antibodies. Objective: We aimed to determine the expression of SSTRs 1, 2a, 3, and 5 in somatotroph adenomas, to correlate expression with clinical characteristics and the response to octreotide, and to ascertain whether preoperative octreotide treatment affected SSTR expression. Design, Setting, Patients: The study included 78 adenomas from patients operated on consecutively during 2000 to 2010. After exclusion of 13 patients, immunohistochemical analysis with rabbit monoclonal antibodies against SSTRs 1, 2a, 3, and 5 (clones UMB-7, -1, -5, and -4) was performed on 65 adenomas. Intervention: Twenty-eight patients received preoperative octreotide, and 37 patients were operated on without pretreatment. Twenty-six patients were randomized to direct surgery (n = 13) or to octreotide pretreatment (n = 13). Main Outcome Measure: SSTR expression was evaluated using a 12-grade scoring system. The responses to the octreotide test dose (GH reduction) and to 6 months of octreotide (IGF-I reduction) were measured. Results: The majority of adenomas showed membranous expression of SSTRs 2a and 5. SSTR2a expression was reduced in the pretreated group and correlated with the acute octreotide test results and the effect of octreotide treatment. In a linear regression model with SSTR2a expression as the determinant, the correlation with the acute test response improved after adjustment for medical pretreatment. Conclusion: Rabbit monoclonal antibodies are reliable markers of SSTRs in somatotroph adenomas. SSTR2a expression correlated with the response to octreotide and was reduced after octreotide treatment, indicating the need for adjustment when SSTR2a expression is correlated with baseline characteristics. Evaluation of SSTR subtypes may be an important aspect of improving the medical treatment for acromegaly.

[359]

**TÍTULO / TITLE:** - Human Noxin is an anti-apoptotic protein in response to DNA damage of A549 non-small cell lung carcinoma.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Nov 10. doi: 10.1002/ijc.28600.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28600](#)

**AUTORES / AUTHORS:** - Won KJ; Im JY; Yun CO; Chung KS; Kim YJ; Lee JS; Jung YJ; Kim BK; Song KB; Kim YH; Chun HK; Jung KE; Kim MH; Won M

**INSTITUCIÓN / INSTITUTION:** - Medical Genomics Research Center, KRIBB, Daejeon, Korea; Functional Genomics, University of Science and Technology, Daejeon, Korea.

**RESUMEN / SUMMARY:** - Human Noxin (hNoxin, C11Orf82), a homolog of mouse noxin, is highly expressed in colorectal and lung cancer tissues. hNoxin contains a DNA-binding C-domain in RPA1, which mediates DNA metabolic processes, such as DNA replication and DNA repair. Expression of hNoxin is associated with S phase in cancer cells and in normal cells. Expression of hNoxin was induced by ultraviolet (UV) irradiation. Knockdown of hNoxin caused growth inhibition of colorectal and lung cancer cells. The comet assay and western blot analysis revealed that hNoxin knockdown induced apoptosis through activation of p38 mitogen-activated protein kinase (MAPK)/p53 in non-small cell lung carcinoma A549 cells. Furthermore, simultaneous hNoxin knockdown and treatment with DNA-damaging agents, such as camptothecin (CPT) and UV irradiation, enhanced apoptosis, whereas Trichostatin A (TSA) did not. However, transient overexpression of hNoxin rescued cells from DNA damage-induced apoptosis but did not block apoptosis in the absence of DNA damage. These results suggest that hNoxin may be associated with inhibition of apoptosis in response to DNA damage. An adenovirus expressing a short hairpin RNA against hNoxin transcripts significantly suppressed the growth of A549 tumor xenografts, indicating that hNoxin knockdown has in vivo anti-tumor efficacy. Thus, hNoxin is a DNA damage-induced anti-apoptotic protein and potential therapeutic target in cancer.

[360]

**TÍTULO / TITLE:** - Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and kidney disease.

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

**REVISTA / JOURNAL:** - Curr Opin Nephrol Hypertens. 2013 Nov 19.

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

[1097/01.mnh.0000437331.23794.81](#)

**AUTORES / AUTHORS:** - Ruiz-Ortega M; Ortiz A; Ramos AM

**INSTITUCIÓN / INSTITUTION:** - aIIS-Fundacion Jimenez Diaz bREDinREN cUniversidad Autonoma de Madrid dIRSIN, Madrid, España.

**RESUMEN / SUMMARY:** - PURPOSE OF REVIEW: The tumor necrosis factor-like weak inducer of apoptosis (TWEAK) cytokine has been linked to kidney injury by functional studies in experimental animals, and has biomarker potential in kidney disease. RECENT FINDINGS: TWEAK was known to promote tubular cell injury and kidney inflammation. Recent studies have expanded these observations, identifying additional targets of TWEAK relevant to kidney injury. Thus, TWEAK upregulates the chemokine and cholesterol scavenger receptor CXCL16 and downregulates the antiaging and

antifibrotic molecule Klotho in tubular cells. Furthermore, fibrogenic TWEAK actions on renal fibroblasts were described. TWEAK or factor-inducible molecule 14 targeting decreased the kidney fibrosis resulting from immune and nonimmune kidney injury induced by transient tubular or glomerular insults or by persistent urinary tract obstruction. TWEAK might also contribute to the link between chronic kidney disease and kidney cancer, as suggested by its role in other genitourinary cancers. Progress has also been made in TWEAK targeting. A phase I clinical trial showed that TWEAK targeting is well tolerated in humans, and an ongoing trial is exploring efficacy in lupus nephritis. Nanomolecules and inhibitors of epidermal growth factor receptor pathway may also protect from the adverse effects of TWEAK in the kidney. SUMMARY: These findings suggest that TWEAK targeting has clinical potential in kidney injury of immune and nonimmune origin.

[361]

**TÍTULO / TITLE:** - Inhibition of PARP1 by small interfering RNA enhances docetaxel activity against human prostate cancer PC3 cells.

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

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Nov 15. pii: S0006-291X(13)01909-8. doi: 10.1016/j.bbrc.2013.11.027.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.bbrc.2013.11.027](#)

**AUTORES / AUTHORS:** - Wu W; Kong Z; Duan X; Zhu H; Li S; Zeng S; Liang Y; Iliakis G; Gui Z; Yang D

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Minimally Invasive Surgery Center, The First Affiliated Hospital of Guangzhou Medical University, Guangdong Key Laboratory of Urology, China. Electronic address: [wwqwml@163.com](mailto:wwqwml@163.com).

**RESUMEN / SUMMARY:** - Though poly(ADP-ribose) polymerase 1 (PARP1) inhibitors have benefits in combination with radiotherapy in prostate cancers, few is known about the exactly role and underlying mechanism of PARP1 in combination with chemotherapy agents. Here our data revealed that inhibition of PARP1 by small interfering RNA (siRNA) could enhance docetaxel's activity against PC3 cells, which is associated with an accelerate repression of EGF/Akt/FOXO1 signaling pathway. Our results provide a novel role of PARP1 in transcription regulation of EGFR/Akt/FOXO1 signaling pathway and indicate that PARP1 siRNA combined with docetaxel can be an innovative treatment strategy to potentially improve outcomes in CRPC patients.

[362]

**TÍTULO / TITLE:** - Selective strong synergism of Ruxolitinib and second generation tyrosine kinase inhibitors to overcome bone marrow stroma related drug resistance in chronic myelogenous leukemia.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Nov 15. pii: S0145-2126(13)00394-9. doi: 10.1016/j.leukres.2013.11.006.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.leukres.2013.11.006](#)

**AUTORES / AUTHORS:** - Quintarelli C; De Angelis B; Errichiello S; Caruso S; Esposito N; Colavita I; Raia M; Pagliuca S; Pugliese N; Risitano AM; Picardi M; Luciano L; Saglio G; Martinelli G; Pane F

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Medicina Clinica e Chirurgia, University of Naples Federico II, Italy; CEINGE Biotechnologie Avanzate, Napoli, Italy. Electronic address: [concetta.quintarelli@unina.it](mailto:concetta.quintarelli@unina.it).

**RESUMEN / SUMMARY:** - The IC50 of TKIs is significantly increased when BCR-ABL+ K562 cell line is cultured in stroma conditioned media produced by BM mesenchymal cells. In particular, while the Imatinib IC50 in the stromal co-cultures was well above the in vivo through levels of the drug, the IC50s of second generation TKIs were still below their through levels. Moreover, we provide a formal comparison of the synergy between first and second generation TKIs with the JAK inhibitor Ruxolitinib to overcome BM stroma related TKI resistance. Taken together, our data provide a rationale for the therapeutic combination of TKIs and Ruxolitinib with the aim to eradicate primary BCR-ABL+ cells homed in BM niches.

[363]

**TÍTULO / TITLE:** - An antiproliferative gene FLNA regulates migration and invasion of gastric carcinoma cell in vitro and its clinical significance.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 16.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-1347-1](#)

**AUTORES / AUTHORS:** - Sun GG; Sheng SH; Jing SW; Hu WN

**INSTITUCIÓN / INSTITUTION:** - Department of Chemoradiotherapy, Tangshan People's Hospital, No. 65, Shengli Road, Lunan District, Tangshan, 063000, Hebei Province, China.

**RESUMEN / SUMMARY:** - This study aimed to analyze the expression and clinical significance of filamin A (FLNA) in gastric carcinoma and the biological effect in its cell line by FLNA overexpression. Immunohistochemistry and western blot were used to analyze FLNA protein expression in 47 cases of gastric cancer and 47 cases of normal tissues to study the relationship between FLNA expression and clinical factors. FLNA lentiviral vector and empty vector were respectively transfected into gastric cancer SGC-7901 cell line. Reverse transcription-polymerase chain reaction (RT-PCR) and western blot were used to detect the mRNA level and protein of FLNA. 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay and migration and invasion assays were also conducted to determine the influence of the upregulated expression of FLNA that might be found on SGC-7901 cell biological effect. Immunohistochemistry: The level of FLNA protein expression was found to be significantly lower in gastric cancer tissue than normal tissues ( $P < 0.05$ ). Western blot: The relative amount of FLNA protein in gastric cancer tissue was found to be significantly lower than in normal tissues ( $P < 0.05$ ). The level of FLNA protein expression was not correlated with gender, age, and tumor invasion ( $P > 0.05$ ), but it was correlated with lymph node metastasis, clinic stage, and histological grade ( $P < 0.05$ ). Loss of FLNA expression correlated significantly with poor overall survival time by Kaplan-Meier analysis ( $P < 0.05$ ). The result of biological function showed that SGC-7901 cell transfected FLNA had a lower survival fraction, significant decrease in migration and invasion, and lower matrix metalloproteinase 9 (MMP-9) protein expression compared with SGC-7901 cell untransfected FLNA ( $P < 0.05$ ). FLNA expression decreased in gastric cancer and correlated significantly with lymph node metastasis, clinic stage, histological grade, and poor overall survival, suggesting that

FLNA may play important roles as a negative regulator to gastric cancer SGC-7901 cell by promoting degradation of MMP-9.

[364]

**TÍTULO / TITLE:** - MicroRNA-23a Antisense Enhances 5-Fluorouracil Chemosensitivity through APAF-1/Caspase-9 Apoptotic Pathway in Colorectal Cancer Cells.

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

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 Nov 19. doi: 10.1002/jcb.24721.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24721](#)

**AUTORES / AUTHORS:** - Shang J; Yang F; Wang Y; Wang Y; Xue G; Mei Q; Wang F; Sun S

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Genetics, Institute of Genetics, Second Military Medical University, Shanghai, China.

**RESUMEN / SUMMARY:** - Current literature provided information that alteration in microRNA expression impacted sensitivity or resistance of certain tumor types to anticancer treatment, including the possible intracellular pathways. The microRNA-23a (miR-23a)-regulated apoptosis in response to the 5-fluorouracil (5-FU)-induced mitochondria-mediated apoptotic pathway was determined in this study. The miR-23a expression in 5-FU-treated and untreated colon cancer cells and tissues was assessed using real-time PCR analysis. To determine the function of miR-23a in the regulation of 5-FU-induced apoptosis, cell-proliferation, cytotoxicity and apoptosis analyses were performed. Dual luciferase reporter assay was used to identify the apoptosis-related target gene for miR-23a. The activity of caspases-3, -7, and -9 were also assessed in miR-23a antisense and 5-FU treated tumor cells. A xenograft tumor model was established to evaluate the biological relevance of altered miR-23a expression to the 5-FU-based chemotherapy in vivo. We found that the expression of miR-23a was increased and the level of apoptosis-activating factor-1 (APAF-1) was decreased in 5-FU-treated colon cancer cells compared to untreated cells. The activation of the caspases-3 and 7 was increased in miR-23a antisense and 5-FU-treated colon cancer cells compared to negative control. APAF-1, as a target gene of miR-23a, was identified and miR-23a antisense-induced increase in the activation of caspase-9 was observed. The overexpression of miR-23a antisense up-regulated the 5-FU induced apoptosis in colon cancer cells. However, the miR-23a knockdown did not increase the antitumor effect of 5-FU in xenograft model of colon cancer. This study shows that miR-23a antisense enhanced 5-FU-induced apoptosis in colorectal cancer cells through the APAF-1/caspase-9 apoptotic pathway. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[365]

**TÍTULO / TITLE:** - The Combinational Effect of Vincristine and Berberine on Growth Inhibition and Apoptosis Induction in Hepatoma Cells.

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

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 Nov 14. doi: 10.1002/jcb.24715.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24715](#)

**AUTORES / AUTHORS:** - Wang L; Wei D; Han X; Zhang W; Fan C; Zhang J; Mo C; Yang M; Li J; Wang Z; Zhou Q; Xiao H

**INSTITUCIÓN / INSTITUTION:** - Lab for Aging Research, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, Keyuan 4-1, Gaopeng Avenue, High-tech Zone, Chengdu, 610041, People's Republic of China.

**RESUMEN / SUMMARY:** - The use of vincristine, a known antitumor agent, in hepatoma therapy is limited particularly because of its toxic effect. Meanwhile, berberine has drawn increasing attention to its antineoplastic effect in recent years. In view of the advantages of combinational drug treatment reported in anti-cancer chemotherapy, we evaluated the effects of co-treatment of vincristine and berberine on hepatic carcinoma cell lines in this study. We find that combinational usage of these two drugs can significantly induce cell growth inhibition and apoptosis even under a concentration of vincristine barely showing cytotoxicity in the same cells when used alone. The underlying mechanism about this combinational effect was addressed in this study by monitoring the signals related to mitochondrial function, apoptotic pathway and endoplasmic reticulum stress. Our results suggest a new value of berberine as a potential adjuvant agent in cancer chemotherapy and provide a hopeful approach for developing hepatoma therapy by utilizing the combinational effect of vincristine and berberine. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[366]

**TÍTULO / TITLE:** - Proteomic characterization of breast cancer xenografts identifies early and late bevacizumab-induced responses and predicts effective drug combinations.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 5.

- Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1865](#)

**AUTORES / AUTHORS:** - Lindholm EM; Krohn M; Iadevaia S; Kristian A; Mills GB; Maelandsmo GM; Engebraaten O

**INSTITUCIÓN / INSTITUTION:** - Tumor biology, Oslo University Hospital, Norwegian Radium Hospital.

**RESUMEN / SUMMARY:** - PURPOSE: Neoangiogenesis is an important feature in tumor growth and progression, and combining chemotherapy and antiangiogenic drugs have demonstrated clinical efficacy. However, as treatment induced resistance often develops our goal was to identify pathways indicating response and/or evolving resistance to treatment, and inhibit these pathways to optimize the treatment strategies. EXPERIMENTAL DESIGN: To identify markers of response and/or resistance Reverse Phase Protein Array (RPPA) was utilized to characterize treatment-induced changes in a bevacizumab responsive and a nonresponsive human breast cancer xenograft. Results were combined with bioinformatic modeling to predict druggable targets for optimization of the treatment. RESULTS: RPPA analysis showed that both tumor models responded to bevacizumab with an early (day 3) upregulation of growth factor receptors and downstream signaling pathways, with persistent mTOR signaling until the end of the in vivo experiment. Adding doxorubicin to bevacizumab showed significant and superior growth inhibition of basal-like tumors, whereas no additive effect was seen in the luminal-like model. The combination treatment corresponded to a continuous late attenuation of mTOR signaling in the basal-like model, while the inhibition was temporary in the luminal-like model. Integrating the

bevacizumab-induced dynamic changes in protein levels with bioinformatic modeling predicted inhibition of PI3K-pathway to increase the efficacy of bevacizumab monotherapy. In vivo experiments combining bevacizumab and the PI3K/mTOR inhibitor BEZ235 confirmed their significant and additive growth inhibitory effect in the basal-like model. CONCLUSIONS: Treatment with bevacizumab caused compensatory upregulation of several signaling pathways. Targeting such pathways increased the efficacy of antiangiogenic therapy.

[367]

**TÍTULO / TITLE:** - Combination of ascorbate/epigallocatechin-3-gallate/gemcitabine synergistically induces cell cycle deregulation and apoptosis in mesothelioma cells.

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

**REVISTA / JOURNAL:** - Toxicol Appl Pharmacol. 2013 Nov 4. pii: S0041-008X(13)00473-0. doi: 10.1016/j.taap.2013.10.025.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.10.025](#)

**AUTORES / AUTHORS:** - Martinotti S; Ranzato E; Parodi M; Vitale M; Burlando B

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale "Amedeo Avogadro", viale T. Michel 11, 15121 Alessandria, Italy.

**RESUMEN / SUMMARY:** - Malignant mesothelioma (MMe) is a poor-prognosis tumor in need of innovative therapies. In a previous in vivo study, we showed synergistic anti-MMe properties of the ascorbate/epigallocatechin-3-gallate/gemcitabine combination. We have now focused on the mechanism of action, showing the induction of apoptosis and cell cycle arrest through measurements of caspase 3, intracellular Ca<sup>2+</sup>, annexin V, and DNA content. StellArray PCR technology and Western immunoblotting revealed DAPK2-dependent apoptosis, upregulation of cell cycle promoters, downregulation of cell cycle checkpoints and repression of NFκB expression. The complex of data indicates that the mixture is synergistic in inducing cell cycle deregulation and non-inflammatory apoptosis, suggesting its possible use in MMe treatment.

[368]

**TÍTULO / TITLE:** - High Expression of Interleukin-22 and Its Receptor Predicts Poor Prognosis in Pancreatic Ductal Adenocarcinoma.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3322-x](#)

**AUTORES / AUTHORS:** - Wen Z; Liao Q; Zhao J; Hu Y; You L; Lu Z; Jia C; Wei Y; Zhao Y

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Tsinghua University, Beijing, China.

**RESUMEN / SUMMARY:** - BACKGROUND: The cytokine interleukin-22 (IL-22) and its receptor are present in the tumor microenvironment. Their function in pancreatic ductal adenocarcinoma (PDAC) remains largely unknown. The goal of the present study was to measure the expression of IL-22 and IL-22R in PDAC and assess their relationship with clinicopathological features and prognosis. METHODS: The expression of IL-22

and IL-22R was evaluated by immunohistochemistry in PDAC tissues from 57 patients and by Western blotting in six tumors and adjacent nontumor tissues. A statistical analysis was conducted to assess the relationship between levels of expression, clinicopathological factors, and overall survival. In addition, the relationship between the expression of IL-22 and IL-22R and invasion was assessed by Western blotting and transwell assay with the PDAC cell lines PANC1 and BxPC3. RESULTS: Positive IL-22 staining was detected in PDAC tissues and adjacent nontumor tissues. Positive IL-22R staining was detected in PDAC cells. High expression of IL-22 and IL-22R correlated significantly with lymph node involvement. IL-22 increased the phosphorylation of signal transducer and activator of transcription3, the expression of matrix metalloproteinase 9, and the invasion in PANC1 and BxPC3 cells in vitro while silencing of IL-22R RNA caused opposite effects. Most importantly, overall survival was significantly poorer in patients with high expression of IL-22 and IL-22R than in those with low expression. CONCLUSIONS: These findings reveal the positive role of IL-22 and IL-22R in invasion and metastasis in human PDAC. IL-22 and IL-22R may be suitable independent prognostic markers in PDAC.

[369]

**TÍTULO / TITLE:** - Mitochondria are the primary target in the induction of apoptosis by chiral ruthenium(II) polypyridyl complexes in cancer cells.

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

**REVISTA / JOURNAL:** - J Biol Inorg Chem. 2013 Nov 28.

•• Enlace al texto completo (gratis o de pago) [1007/s00775-013-1069-2](#)

**AUTORES / AUTHORS:** - Wang JQ; Zhang PY; Qian C; Hou XJ; Ji LN; Chao H

**INSTITUCIÓN / INSTITUTION:** - MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, State Key Laboratory of Optoelectronic Materials and Technologies, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou, 510275, People's Republic of China.

**RESUMEN / SUMMARY:** - A series of novel chiral ruthenium(II) polypyridyl complexes (Delta-Ru1, Lambda-Ru1, Delta-Ru2, Lambda-Ru2, Delta-Ru3, Lambda-Ru3) were synthesized and evaluated to determine their antiproliferative activities. Colocalization, inductively coupled plasma mass spectrometry, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay studies showed that these ruthenium(II) complexes accumulated preferentially in the mitochondria and exhibited cytotoxicity against various cancer cells in vitro. The complex Delta-Ru1 is of particular interest because it was found to have half-maximal inhibitory concentrations comparable to those of cisplatin and better activity than cisplatin against a cisplatin-resistant cell line, A549-CP/R. Delta-Ru1 induced alterations in the mitochondrial membrane potential and triggered intrinsic mitochondria-mediated apoptosis in HeLa cells, which involved the regulation of Bcl-2 family members and the activation of caspases. Taken together, these data suggest that Delta-Ru1 may be a novel mitochondria-targeting anticancer agent.

[370]

**TÍTULO / TITLE:** - Antiproliferative and apoptosis-inducing activity of an oxidovanadium(IV) complex with the flavonoid silibinin against osteosarcoma cells.

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

**REVISTA / JOURNAL:** - J Biol Inorg Chem. 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [1007/s00775-013-1061-x](#)

**AUTORES / AUTHORS:** - Leon IE; Porro V; Di Virgilio AL; Naso LG; Williams PA; Bollati-Fogolin M; Etcheverry SB

**INSTITUCIÓN / INSTITUTION:** - Catedra de Bioquímica Patológica, Facultad Ciencias Exactas, Universidad Nacional de La Plata, 47 y 115, 1900, La Plata, Argentina.

**RESUMEN / SUMMARY:** - Flavonoids are a large family of polyphenolic compounds synthesized by plants. They display interesting biological effects mainly related to their antioxidant properties. On the other hand, vanadium compounds also exhibit different biological and pharmacological effects in cell culture and in animal models. Since coordination of ligands to metals can improve or change the pharmacological properties, we report herein, for the first time, a detailed study of the mechanisms of action of an oxidovanadium(IV) complex with the flavonoid silibinin, Na<sub>2</sub>[VO(silibinin)<sub>2</sub>].6H<sub>2</sub>O (VOsil), in a model of the human osteosarcoma derived cell line MG-63. The complex inhibited the viability of osteosarcoma cells in a dose-dependent manner with a greater potency than that of silibinin and oxidovanadium(IV) (p < 0.01), demonstrating the benefit of complexation. Cytotoxicity and genotoxicity studies also showed a concentration effect for VOsil. The increase in the levels of reactive oxygen species and the decrease of the ratio of the amount of reduced glutathione to the amount of oxidized glutathione were involved in the deleterious effects of the complex. Besides, the complex caused cell cycle arrest and activated caspase 3, triggering apoptosis as determined by flow cytometry. As a whole, these results show the main mechanisms of the deleterious effects of VOsil in the osteosarcoma cell line, demonstrating that this complex is a promising compound for cancer treatments.

[371]

**TÍTULO / TITLE:** - Inhibition of type I insulin-like growth factor receptor tyrosine kinase by picropodophyllin induces apoptosis and cell cycle arrest in T lymphoblastic leukemia/lymphoma.

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

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

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.862241](#)

**AUTORES / AUTHORS:** - Huang Z; Fang Z; Zhen H; Zhou L; Amin HM; Shi P

**RESUMEN / SUMMARY:** - Abstract It has been recently shown that IGF-IR contributes significantly to the survival of T lymphoblastic leukemia/lymphoma (T-LBL) cells, and it was therefore suggested that IGF-IR could represent a legitimate therapeutic target in this aggressive disease. Picropodophyllin (PPP) is a potent, selective inhibitor of IGF-IR that is currently used with notable success in clinical trials that include patients with aggressive types of epithelial tumors. In the present study, we tested the effects of PPP on Jurkat and Molt-3 cells; two prototype T-LBL cell lines. Our results demonstrate that PPP efficiently induced apoptotic cell death and cell cycle arrest of these two cells. These effects were attributable to alterations of downstream target proteins. By using proteomic analysis, 7 different proteins were found to be affected by PPP treatment of Jurkat cells. These proteins are involved in various aspects of cellular metabolism, cytoskeleton organization, and signal transduction pathways. The results suggest that

PPP affects multiple signaling molecules and inhibits fundamental pathways that control cell growth and survival. Our study also provides novel evidence that PPP could be potentially utilized for the treatment of the aggressive T-LBL.

[372]

**TÍTULO / TITLE:** - Bruton tyrosine kinase inhibitors: a promising novel targeted treatment for B cell lymphomas.

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

**REVISTA / JOURNAL:** - Br J Haematol. 2013 Nov;163(4):436-43. doi: 10.1111/bjh.12573. Epub 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1111/bjh.12573](#)

**AUTORES / AUTHORS:** - Aalipour A; Advani RH

**INSTITUCIÓN / INSTITUTION:** - Stanford University Medical Center, Stanford, CA, USA.

**RESUMEN / SUMMARY:** - Constitutive or aberrant signalling of the B cell receptor signalling cascade has been implicated in the propagation and maintenance of a variety of B cell malignancies. Small molecule inhibitors of Bruton tyrosine kinase (BTK), a protein early in this cascade and specifically expressed in B cells, have emerged as a new class of targeted agents. There are several BTK inhibitors, including ONO-WG-307, LFM-A13, dasatinib, CC-292, and PCI-32765 (ibrutinib), in preclinical and/or clinical development of which ibrutinib is currently in phase III trials. Recent clinical data suggest significant activity of ibrutinib as a first in class oral inhibitor of BTK. This review provides an overview of ongoing clinical studies of BTK inhibitors.

[373]

**TÍTULO / TITLE:** - The prognostic value of apoptotic and proliferative markers in breast cancer.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Nov;142(2):323-39. doi: 10.1007/s10549-013-2748-y. Epub 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2748-y](#)

**AUTORES / AUTHORS:** - Engels CC; Ruberta F; de Kruijf EM; van Pelt GW; Smit VT; Liefers GJ; Matsushima T; Shibayama M; Ishihara H; van de Velde CJ; Kuppen PJ

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Leiden University Medical Center, Albinusdreef 2, 2300 RC, Leiden, The Netherlands.

**RESUMEN / SUMMARY:** - Increasing ability of early breast cancer (BC) diagnosis leading to more early stage detection, better survival, and low relapse marks one of the milestones achieved over the decades. Foregoing poses a challenge for clinicians regarding optimal treatment, in which over- and under-treatment should be avoided. Classical prognostic and predictive factors fall short for individualized adjuvant therapy selection in this patient group. The key to better characterization may be found in the biology underlying individual tumors. We hypothesized that markers related to cellular proliferation and apoptosis and the balance between these two processes in tumor development will be predictive for clinical outcome. Our study population (N = 822) consisted of all early stage BC patients primarily treated with surgery in our center between 1985 and 1996. Sections of available tumor tissue (87 %, 714/822) were immunohistochemically stained for expression of p53, active-caspase-3, and Ki67. In

43 % (304/714) and 18 % (126/714) of this cohort, respectively, a biochemical C2P(®) risk prediction and caspase-3 assay were performed. Expression data of the mentioned markers, single, or combined, were analyzed. Results showed that both the single and combined markers, whether of apoptotic or proliferative origin had associations with clinical outcome. An additive effect was seen for the hazard ratios when data on p53, active caspase-3, and Ki67 status were combined. The assembled prognostic apoptotic-proliferative subtype showed significant association for both the overall survival ( $p = 0.024$ ) and relapse-free period ( $p = 0.001$ ) in the multivariate analyses of grade I breast tumors. Combined markers of tumor cell apoptosis and proliferation represent tumor aggressiveness. The apoptotic-proliferative subtypes that we present in this study represent a clinical prognostic profile with solid underlying biological rationale and pose a promising method for accurate identification of grade I BC patients in need of an aggressive therapeutic approach, thus contributing to precision medicine in BC disease.

[374]

**TÍTULO / TITLE:** - Combination therapy with tumor necrosis factor inhibitors in psoriasis treatment.

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

**REVISTA / JOURNAL:** - Cutis. 2013 Sep;92(3):140-7.

**AUTORES / AUTHORS:** - Famenini S; Wu JJ

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, Kaiser Permanente Los Angeles Medical Center, 1515 N Vermont Ave, 5th Floor, Los Angeles, CA 90027, USA. [jashinwu@hotmail.com](mailto:jashinwu@hotmail.com).

**RESUMEN / SUMMARY:** - Psoriasis is a systemic disease that affects approximately 2% of the US population. Traditional treatment modalities include phototherapy, topical therapy, methotrexate, cyclosporine, and retinoids. Three tumor necrosis factor (TNF) inhibitors have been approved by the US Food and Drug Administration for the treatment of plaque psoriasis: etanercept, infliximab, and adalimumab. The combination of TNF inhibitors with phototherapy and topical and systemic agents may be effective in treating patients who are recalcitrant to monotherapy. We examine clinical trials that evaluated the efficacy and safety of combination treatments with TNF inhibitors. This review elucidates that combination therapy is both effective and well tolerated among patients with refractory psoriasis. Furthermore, combination therapy may allow for reduction of required treatment doses, thereby decreasing the potential for toxicity. It is important to note, however, that the studies reviewed here are limited in the long-term follow-up of patients. We conclude that dermatologists can safely and effectively incorporate combination therapy with TNF inhibitors in the treatment of patients with recalcitrant psoriasis.

[375]

**TÍTULO / TITLE:** - Dietary polyacetylenes of the falcarinol type are inhibitors of breast cancer resistance protein (BCRP/ABCG2).

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

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 Nov 20. pii: S0014-2999(13)00852-2. doi: 10.1016/j.ejphar.2013.11.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejphar.2013.11.005](https://doi.org/10.1016/j.ejphar.2013.11.005)

**AUTORES / AUTHORS:** - Tan KW; Killeen DP; Li Y; Paxton JW; Birch NP; Scheepens A

**INSTITUCIÓN / INSTITUTION:** - Food Innovation, The New Zealand Institute for Plant & Food Research Limited, Auckland 1142, New Zealand; School of Biological Sciences, Faculty of Science, The University of Auckland, Auckland, New Zealand; Department of Pharmacology and Clinical Pharmacology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand. Electronic address: [kee.tan@plantandfood.co.nz](mailto:kee.tan@plantandfood.co.nz).

**RESUMEN / SUMMARY:** - Polyacetylenes of the falcarinol type are present in vegetables such as carrots and parsley. They display interesting bioactivities and hold potential as health-promoting and therapeutic agents. In this study, falcarinol, falcarindiol, falcarindiol 3-acetate and falcarindiol 3,8-diacetate were examined for their modulation on breast cancer resistance protein (BCRP/ABCG2), an efflux transporter important for xenobiotic absorption and disposition, and multidrug resistance in cancer. Falcarinol, falcarindiol, and falcarindiol 3-acetate were extracted from carrots and falcarindiol 3,8-diacetate prepared from falcarindiol. Their modulatory effects on ABCG2 were studied using three methods-mitoxantrone accumulation, vesicular transport, and ATPase assay. The polyacetylenes inhibited mitoxantrone (an ABCG2 substrate) efflux in ABCG2-overexpressing HEK293 cells. The inhibitory effect was confirmed in the vesicular transport assay, in which concentration-dependent inhibition of methotrexate (an ABCG2 substrate) uptake into ABCG2-overexpressing Sf9 membrane vesicles was observed (IC<sub>50</sub>=19.7-41.7µM). The polyacetylenes also inhibited baseline and sulfasalazine-stimulated vanadate-sensitive ATPase activities in ABCG2-overexpressing Sf9 membrane vesicles (IC<sub>50</sub>=19.3-79.3µM). This is the first report of an inhibitory effect of polyacetylenes on ABCG2. These results indicate a prospective use of polyacetylenes as multidrug resistance reversal agents, a possible role of ABCG2 in the absorption and disposition of polyacetylenes, and potential food-drug interactions between polyacetylene-rich foods and ABCG2 substrate drugs.

[376]

**TÍTULO / TITLE:** - ALK gene amplification is associated with poor prognosis in colorectal carcinoma.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 12;109(10):2735-43. doi: 10.1038/bjc.2013.641. Epub 2013 Oct 15.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.641](https://doi.org/10.1038/bjc.2013.641)

**AUTORES / AUTHORS:** - Bavi P; Jehan Z; Bu R; Prabhakaran S; Al-Sanea N; Al-Dayel F; Al-Assiri M; Al-Halouly T; Sairafi R; Uddin S; Al-Kuraya KS

**INSTITUCIÓN / INSTITUTION:** - Human Cancer Genomic Research, Research Center, King Faisal Specialist Hospital and Research Center, Riyadh 11211, Saudi Arabia.

**RESUMEN / SUMMARY:** - Background:Recently, the anaplastic lymphoma kinase (ALK) has been found to be altered in several solid and haematological tumours. ALK gene copy number changes and mutations in colorectal cancers (CRCs) are not well characterised. We aimed to study the prevalence of ALK copy number changes, translocations, gene mutations and protein expression in 770 CRC patients, and correlate these findings with molecular and clinico-pathological data.Methods:ALK

gene copy number variations and ALK expression were evaluated by fluorescence in situ hybridisation (FISH) and immunohistochemistry, respectively. Results: Translocations of the ALK gene were not observed; 3.4% (26 out of 756) of the CRC patients tested had an increase in ALK gene copy number either amplification or gain. Interestingly, increased ALK gene copy number alteration was associated with poor prognosis (P=0.0135) and was an independent prognostic marker in multivariate Cox proportional hazards model. The study reveals a significant impact of ALK gene copy number alterations on the outcome of patients with CRC. Conclusion: The findings of our study highlight a potential role of targeting ALK in advanced CRCs by using ALK FISH and ALK IHC as a screening tool to detect ALK alterations. Based on these findings, a potential role of ALK inhibitor as a therapeutic agent in a subset of CRC merits further investigation.

[377]

**TÍTULO / TITLE:** - A combination of pterostilbene with autophagy inhibitors exerts efficient apoptotic characteristics in both chemosensitive and chemoresistant lung cancer cells.

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

**REVISTA / JOURNAL:** - Toxicol Sci. 2013 Oct 23.

●● [Enlace al texto completo \(gratis o de pago\) 1093/toxsci/kft238](#)

**AUTORES / AUTHORS:** - Hsieh MJ; Lin CW; Yang SF; Sheu GT; Yu YY; Chen MK; Chiou HL

**INSTITUCIÓN / INSTITUTION:** - Cancer Research Center, Changhua Christian Hospital, Changhua 500, Taiwan.

**RESUMEN / SUMMARY:** - The emergence of multidrug resistance (MDR), meaning that cancer cells develop simultaneous resistance to different drugs, has limited the clinical efficacy and application of chemotherapy. Pterostilbene, a naturally occurring phytoalexin exerts a variety of pharmacologic activities, including antioxidation, cancer prevention and cytotoxicity to various cancer cells. In this study, results approved the capability of pterostilbene to effectively inhibit the cell growth of docetaxel-induced multidrug resistance human lung cancer cells lines and such inhibition is through an induction of cell cycle arrest and apoptosis. Meanwhile, the observation of the formation of acidic vesicular organelles and LC3-II production revealed an induction of autophagy at an early stage by pterostilbene, which was triggered by an inhibition of the AKT and JNK and an activation of the ERK1/2 pathway. Furthermore, an inhibition of autophagy by pretreatment with 3-methyladenine, bafilomycin A1 or Beclin 1 siRNA was able to enhance pterostilbene-triggered apoptosis. In conclusion, this study demonstrate that pterostilbene causes autophagy and apoptosis in lung cancer cells. Furthermore, a combination of pterostilbene with autophagy inhibitors may strengthen the efficiency of proapoptotic chemotherapeutic strategies in both chemosensitive and chemoresistant lung cancer cells, which may be of great value for the clinical management of lung cancer patients with multidrug resistance.

[378]

**TÍTULO / TITLE:** - The MicroRNA-21/PTEN Pathway Regulates the Sensitivity of HER2-Positive Gastric Cancer Cells to Trastuzumab.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3325-7](#)

**AUTORES / AUTHORS:** - Eto K; Iwatsuki M; Watanabe M; Ida S; Ishimoto T; Iwagami S; Baba Y; Sakamoto Y; Miyamoto Y; Yoshida N; Baba H

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: The ToGA trial demonstrated the significant efficacy of trastuzumab in addition to chemotherapy in patients with HER2-positive gastric cancer (GC). Although trastuzumab has become a key drug in breast cancer treatment, resistance to trastuzumab is a major problem in clinical practice. The aim of the current study was to identify the micro-RNA (miR)/gene pathway regulating the sensitivity of HER2-positive GC cells to trastuzumab. METHODS: Correlations between the expression levels of miR-21, PTEN, and p-AKT were analyzed by real-time PCR and Western blot test in HER2-positive GC cell lines. The effects of overexpression or suppression of miR-21 on the sensitivity of GC cells to trastuzumab were also analyzed in vitro. RESULTS: Overexpression of miR-21 down-regulated PTEN expression, increased AKT phosphorylation, and did not affect HER2 expression. Inversely, suppression of miR-21 increased PTEN expression and down-regulated AKT phosphorylation, but still did not affect HER2 expression. Overexpression of miR-21 decreased the sensitivity of GC cells to trastuzumab, while suppression of miR-21 expression restored the resistance of GC cells to trastuzumab. Overexpression of miR-21 significantly suppressed trastuzumab-induced apoptosis. CONCLUSIONS: To our knowledge, this study was the first reveal the miR-21/PTEN pathway regulated the sensitivity of HER2-positive GC cell lines to trastuzumab through modulation apoptosis. These findings suggest that this pathway may be crucial to the mechanism of resistance to trastuzumab in GC, which may lead to the development of individualized treatment in clinical practice.

[379]

**TÍTULO / TITLE:** - Procyanidin B2 3,3-di-O-gallate, a Biologically Active Constituent of Grape Seed Extract, Induces Apoptosis in Human Prostate Cancer Cells Via Targeting NF-kappaB, Stat3, and AP1 Transcription Factors.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.783602](#)

**AUTORES / AUTHORS:** - Tyagi A; Raina K; Shrestha SP; Miller B; Thompson JA; Wempe MF; 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:** - Recently, we identified procyanidin B2 3,3'-di-O-gallate (B2G2) as most active constituent of grape seed extract (GSE) for efficacy against prostate cancer (PCa). Isolating large quantities of B2G2 from total GSE is labor intensive and expensive, thereby limiting both efficacy and mechanistic studies with this novel anticancer agent. Accordingly, here we synthesized gram-scale quantities of B2G2, compared it with B2G2 isolated from GSE for possible equivalent biological

activity and conducted mechanistic studies. Both B2G2 preparations inhibited cell growth, decreased clonogenicity, and induced cell cycle arrest and apoptotic death, comparable to each other, in various human PCa cell lines. Mechanistic studies focusing on transcription factors involved in apoptotic and survival pathways revealed that B2G2 significantly inhibits NF-kappaB and activator protein1 (AP1) transcriptional activity and nuclear translocation of signal transducer and activator of transcription3 (Stat3) in PCa cell lines, irrespective of their functional androgen receptor status. B2G2 also decreased survivin expression which is regulated by NF-kappaB, AP1, and Stat3 and increased cleaved PARP level. In summary, we report B2G2 chemical synthesis at gram-quantity with equivalent biological efficacy against human PCa cell lines and same molecular targeting profiles at key transcription factors level. The synthetic B2G2 will stimulate more research on prostate and possibly other malignancies in preclinical models and clinical translation.

[380]

**TÍTULO / TITLE:** - Large-scale Analysis of PDGFRA Mutations in Melanomas and Evaluation of Their Sensitivity to Tyrosine Kinase Inhibitors Imatinib and Crenolanib.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1266](#)

**AUTORES / AUTHORS:** - Dai J; Kong Y; Si L; Chi Z; Cui C; Sheng X; Mao L; Li S; Lian B; Yang R; Liu S; Xu X; Guo J

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; and Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

**RESUMEN / SUMMARY:** - PURPOSE: Platelet-derived growth factor receptor alpha (PDGFRA) is a target for tyrosine kinase inhibitor (TKI)-based targeted therapy. Dysregulation of PDGFRA has been reported in many cancers. However, PDGFRA mutations in melanomas have not been well studied. We analyzed the genetic mutations of PDGFRA in Chinese patients with melanoma and determined the inhibitory potency of TKIs, such as imatinib and crenolanib, on mutant PDGFRA. EXPERIMENTAL DESIGN: Of note, 351 melanoma tissue samples were examined for genetic mutations in exons 12, 14, and 18 of PDGFRA. Activities of mutations in response to imatinib and crenolanib were analyzed by Western blotting of tyrosine-phosphorylated PDGFRA and cell proliferation assays. RESULTS: PDGFRA mutations were observed in 4.6% (16 of 351) of melanomas, and these mutations were mainly detected in acral and mucosal melanomas. PDGFRA mutations seem to be mutually exclusive with KIT mutations, but may coexist with BRAF and NRAS mutations. The genetic mutations of PDGFRA were unrelated to the age, thickness, and ulceration status of primary melanomas. Thirteen mutations were not reported before, and five (P577S, V658A, R841K, H845Y, and G853D) of them resulted in strong autophosphorylation of PDGFRA. Crenolanib showed higher potency than imatinib in inhibiting the kinase activity of PDGFRA. Except that V658A mutation was imatinib-resistant, all the other mutations were sensitive to both imatinib and

crenolanib. CONCLUSIONS: PDGFRA mutations are detected in a small population of melanoma patients. Our study suggests that patients with melanoma harboring certain PDGFRA mutations may benefit from imatinib and crenolanib treatment. Clin Cancer Res; 1-8. ©2013 AACR.

[381]

**TÍTULO / TITLE:** - Anticancer Bioactive Peptide-3 Inhibits Human Gastric Cancer Growth by Suppressing Gastric Cancer Stem Cells.

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

**REVISTA / JOURNAL:** - J Cell Biochem. 2013 Nov 11. doi: 10.1002/jcb.24711.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24711](#)

**AUTORES / AUTHORS:** - Yu L; Yang L; An W; Su X

**INSTITUCIÓN / INSTITUTION:** - Department of Cell Biology, Capital Medical University, 10 You An Men Wai Street, Fengtai District, Beijing, 100069, China.

**RESUMEN / SUMMARY:** - In the present study, the effective components of anticancer bioactive peptide-3 (ACBP-3), a novel antitumor agent isolated from goat liver, were analyzed. The CD44 (+) fraction of the human gastric cancer cell line was isolated, and the cells within this fraction that could form spheroid colonies (SCs) were identified as gastric cancer stem cells (GCSCs). Subsequently, the antitumor effect of ACBP-3 on GCSCs was investigated in vitro and in vivo. ACBP-3 dose-dependently decreased the percentage of CD44 (+) cells, suppressed the proliferation of the SC cells and inhibited their clone-forming capacity. Tumor formation from inoculated SC cells took substantially longer when the cells were treated with ACBP-3 in vivo. ACBP-3 alone or in combination with cisplatin suppressed xenograft tumor growth. The antitumor efficacy of cisplatin, when combined with ACBP-3, was enhanced even using half of the normal cisplatin dosage. The combination of cisplatin and ACBP-3 could partially alleviate the body weight loss in the mice. Moreover, treatment with ACBP-3 alone could prevent the body weight loss in the mice. Our study indicated that ACBP-3 inhibited gastric cancer cell growth by suppressing the proliferation of CSCs. ACBP-3 could be a potential CSC-targeting agent, and combined with cisplatin therapy, might be an effective way to clinically treat patients with cancer with a lower dose and reduced toxicity. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[382]

**TÍTULO / TITLE:** - Curcumin-loaded nanoparticles enhance apoptotic cell death of U2OS human osteosarcoma cells through the Akt-Bad signaling pathway.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):238-46. doi: 10.3892/ijo.2013.2175. Epub 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2175](#)

**AUTORES / AUTHORS:** - Peng SF; Lee CY; Hour MJ; Tsai SC; Kuo DH; Chen FA; Shieh PC; Yang JS

**INSTITUCIÓN / INSTITUTION:** - Department of Biological Science and Technology, China Medical University, Taichung 404, Taiwan, R.O.C.

**RESUMEN / SUMMARY:** - Curcumin has potential anticancer activity and has been shown to be involved in several signaling pathways including differentiation and

apoptosis. Our previous study showed that water-soluble PLGA curcumin nanoparticles (Cur-NPs) triggered apoptotic cell death through regulation of the function of MDR1 and the production of reactive oxygen species (ROS) in cisplatin-resistant human oral cancer CAR cells. In this study, we investigated the anti-proliferative effects of Cur-NPs on human osteosarcoma U2OS cells. The morphology of Cur-NPs showed spherical shape by TEM analysis. The encapsulation efficiency of curcumin in Cur-NPs prepared by single emulsion was 90.5+/-3.0%. Our results demonstrated that the curcumin fragments on the mass spectrum of Cur-NPs and the peaks of curcumin standard could be found on the Cur-NPs spectrum by 1H-NMR spectra analysis. Cur-NPs induced anti-proliferative effects and apoptosis in U2OS cells. Compared to the untreated U2OS cells, more detectable amount of Cur-NPs was found inside the treated U2OS cells. Cur-NPs induced DNA fragmentation and apoptotic bodies in U2OS cells. Both the activity and the expression levels of caspases-3/-7 and caspase-9 were elevated in the treated U2OS cells. Cur-NPs upregulated the protein expression levels of cleaved caspase-3/caspase-9, cytochrome c, Apaf-1 and Bad and downregulated the protein expression level of p-Akt in U2OS cells. These results suggest Cur-NPs are effective in enhancing apoptosis in human osteosarcoma cells and thus could provide potential for cancer therapeutics.

[383]

**TÍTULO / TITLE:** - Local Anesthetics Induce Apoptosis in Human Breast Tumor Cells.

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

**REVISTA / JOURNAL:** - Anesth Analg. 2013 Nov 15.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1213/ANE.0b013e3182a94479](#)

**AUTORES / AUTHORS:** - Chang YC; Liu CL; Chen MJ; Hsu YW; Chen SN; Lin CH; Chen CM; Yang FM; Hu MC

**INSTITUCIÓN / INSTITUTION:** - From the \*Graduate Institute of Physiology, National Taiwan University College of Medicine; daggerDepartment of Surgery, Mackay Memorial Hospital; double daggerMackay Junior College of Medicine, Nursing, and Management, Taipei; section signMackay Medical College, New Taipei City; and Departments of ||Anesthesiology, and paragraph signMedical Research, Mackay Memorial Hospital, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - **BACKGROUND:** Previous studies have shown that local anesthetics may induce apoptosis in some cell types. In this study, we investigated the apoptotic effects of local anesthetics in human breast tumor cells. **METHODS:** Human breast cancer (MCF-7) and mammary epithelial (MCF-10A) cell lines were treated with lidocaine and/or bupivacaine. Cell viability, DNA fragmentation, and annexin V immunofluorescence staining were assessed. The effects on apoptosis-related protein expression were investigated by Western blot analysis. The findings were extended to studies in an in vivo xenograft model. **RESULTS:** Treatment of breast tumor cells with lidocaine and bupivacaine resulted in inhibition of cell viability via induction of apoptosis. The effects were more prominent in MCF-7 cells than in MCF-10A cells. Treatment with local anesthetics induced caspase 7, 8, 9, and poly ADP-ribose polymerase cleavage. The cleavage of caspase 7 and poly ADP-ribose polymerase induced by local anesthetics were effectively blocked by caspase inhibitors. Furthermore, treatment of MCF-7 xenografts with local anesthetics resulted in higher

expression of cleaved caspase 7 and an increase in terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining. CONCLUSION:: Lidocaine and bupivacaine induce apoptosis of breast tumor cells at clinically relevant concentrations. Our results reveal previously unrecognized beneficial actions of local anesthetics and call for further studies to assess the oncologic advantages of their use during breast cancer surgery.

[384]

**TÍTULO / TITLE:** - Inhibition of focal adhesion kinase induces apoptosis in human osteosarcoma SAOS-2 cells.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1214-0](#)

**AUTORES / AUTHORS:** - Wang J; Zu J; Xu G; Zhao W; Jinglong Y

**INSTITUCIÓN / INSTITUTION:** - Department of Bone Surgery, First Affiliated Hospital of Harbin Medical University, No. 23 Youzheng street, Harbin, Heilongjiang province, 150001, China.

**RESUMEN / SUMMARY:** - Focal adhesion kinase (FAK), a non-receptor tyrosine kinase protein, acts as an early modulator of integrin signaling cascade, regulating basic cellular functions. In transformed cells, unopposed FAK signaling has been considered to promote tumor growth, progression, and metastasis. The aim of this study was to assess the role of focal adhesion kinase in human osteosarcoma SAOS-2 cells. SAOS-2 cells were transfected with PGPU6/GFP/shNC, and PGPU6/GFP/FAK-334 (shRNA-334), respectively. Expression of FAK was detected by real-time PCR and western blots. MTT assay was used to examine changes in cell proliferation. Cell apoptosis was analyzed by flow cytometry. The expression of caspase-3,-7,-9 was measured by Western blots. The expression of FAK in SAOS-2 cells significantly decreased in shRNA-334 group contrast to the control group ( $P < 0.01$ ). Cells proliferation was inhibited by shRNA-334 and shRNA-334 + cisplatin, and the effects were clearly enhanced when cells treated with the anticancer agents. The level of cell apoptosis in shRNA-334 and shRNA-334 + cisplatin group was higher than in the control group ( $P < 0.01$ ). The current data support evidence that down-regulation of FAK could induce SAOS-2 apoptosis through the caspase-dependent cell death pathway. Inhibition of the kinases may be important for therapies designed to enhance the apoptosis in osteosarcoma.

[385]

**TÍTULO / TITLE:** - Vitamin D Analog EB1089 Induces Apoptosis in a Subpopulation of SGC-7901 Gastric Cancer Cells Through a Mitochondrial-Dependent Apoptotic Pathway.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Oct;65(7):1067-75. doi: 10.1080/01635581.2013.811273. Epub 2013 Oct 7.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.811273](#)

**AUTORES / AUTHORS:** - Wang W; Zhao CH; Zhang N; Wang J

**INSTITUCIÓN / INSTITUTION:** - a Department of Pathophysiology, College of Basic Medical Science , China Medical University , Shenyang , China.

**RESUMEN / SUMMARY:** - Gastric cancer is the second leading cause of cancer death worldwide. Cancer stem-like side population (SP) cells may be important factors that hinder efficacy of chemopreventative and chemotherapeutic approaches in gastric cancer. EB1089 is an antitumor agent that has been used in many cancers; however, no reports to date have determined the effects of EB1089 in gastric cancer. In our study, SP and main population (MP) cells were isolated from 4 gastric cancer cell lines in different stages of differentiation by flow cytometry (FCM) and confirmed by reverse transcription polymerase chain reaction (RT-PCR) and Western blot. EB1089 decreased the proliferation, increased apoptosis, and induced mitochondrial damage in the SP cells isolated from 1 cell type (SGC-7901), but not MP cells, through increased Bax and decreased Bcl-2 and Bcl-xL protein expression. This protein expression pattern induced the activation of caspase-3 and caspase-9. The effects of EB1089 on SGC-7901 SP cells were blocked by treating cells with vitamin D receptor (VDR) siRNA or butin (an inhibitor of the mitochondrial apoptosis pathway). Our results suggest that EB1089 targets SGC-7901 SP cells through a mitochondrial apoptosis pathway. However, further studies are needed to elucidate the signal transduction between VDR and the mitochondrial apoptosis pathway.

[386]

**TÍTULO / TITLE:** - p62/SQSTM1 is required for cell survival of apoptosis-resistant bone metastatic prostate cancer cell lines.

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

**REVISTA / JOURNAL:** - Prostate. 2013 Sep 30. doi: 10.1002/pros.22737.

●● Enlace al texto completo (gratis o de pago) [1002/pros.22737](#)

**AUTORES / AUTHORS:** - Chang MA; Morgado M; Warren CR; Hinton CV; Farach-Carson MC; Delk NA

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Cell Biology, Rice University, BioScience Research Collaborative, Houston, Texas.

**RESUMEN / SUMMARY:** - BACKGROUND: Bone marrow stromal cell (BMSC) paracrine factor(s) can induce apoptosis in bone metastatic prostate cancer (PCa) cell lines. However, the PCa cells that escape BMSC-induced apoptosis can upregulate cytoprotective autophagy. METHODS: C4-2, C4-2B, MDA PCa 2a, MDA PCa 2b, VCaP, PC3, or DU145 PCa cell lines were grown in BMSC conditioned medium and analyzed for mRNA and/or protein accumulation of p62 (also known as sequestome-1/SQSTM1), Microtubule-associated protein 1 light chain 3B (LC3B), or lysosomal-associated membrane protein 1 (LAMP1) using quantitative polymerase chain reaction (QPCR), Western blot, or immunofluorescence. Small interfering RNA (siRNA) was used to determine if p62 is necessary PCa cell survival. RESULTS: BMSC paracrine signaling upregulated p62 mRNA and protein in a subset of the PCa cell lines. The PCa cell lines that were insensitive to BMSC-induced apoptosis and autophagy induction had elevated basal p62 mRNA and protein. In the BMSC-insensitive PCa cell lines, siRNA knockdown of p62 was cytotoxic and immunostaining showed perinuclear clustering of autolysosomes. However, in the BMSC-sensitive PCa cell lines, p62 siRNA knockdown was not appreciably cytotoxic and did not affect autolysosome subcellular localization. CONCLUSIONS: A pattern emerges wherein the BMSC-

sensitive PCa cell lines are known to be osteoblastic and express the androgen receptor, while the BMSC-insensitive PCa cell lines are characteristically osteolytic and do not express the androgen receptor. Furthermore, BMSC-insensitive PCa may have evolved a dependency on p62 for cell survival that could be exploited to target and kill these apoptosis-resistant PCa cells in the bone. Prostate © 2013 Wiley Periodicals, Inc.

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**TÍTULO / TITLE:** - Epigenetic regulation of the pro-apoptosis gene TSSC3 in human osteosarcoma cells.

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

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Oct 18. pii: S0753-3322(13)00118-2. doi: 10.1016/j.biopha.2013.10.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.biopha.2013.10.006](http://1016/j.biopha.2013.10.006)

**AUTORES / AUTHORS:** - Li Y; Huang Y; Lv Y; Meng G; Guo QN

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China.

**RESUMEN / SUMMARY:** - Promoter hypermethylation can lead to a loss of genetic imprinting in carcinogenesis. The mechanism for the loss of expression of the imprinted gene TSSC3 has not been investigated in cases of osteosarcoma. In this study, we treated osteosarcoma cell lines with 5-Aza-CdR, which is a widely-used DNA methyltransferase inhibitor, and found dose-dependent reduction in cell growth, conversion of cell morphology to a non-motile phenotype, and obvious increase in apoptosis. In addition, we also found that 5-Aza-CdR reactivated TSSC3 expression through demethylation of the promoter regions. These findings indicate that the TSSC3 gene is silenced through hypermethylation of the promoter regions, a mechanism commonly associated with gene silencing in cancer. Finally, we examined the role of TSSC3 in human osteosarcoma SaOS2 cells. We showed that TSSC3 overexpression suppressed SaOS2 cell growth and increased apoptosis through caspase-3 upregulation, thereby, suggesting that TSSC3 may play a pro-apoptosis role to maintain the normal balance of growth. Taken together, these observations suggest that the epigenetic regulation of TSSC3, a pro-apoptosis gene, provides valuable insights into possible osteosarcoma therapies.

[388]

**TÍTULO / TITLE:** - Loss of NAPRT1 Expression by Tumor-Specific Promoter Methylation Provides a Novel Predictive Biomarker for NAMPT Inhibitors.

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

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

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-](http://1158/1078-0432.CCR-13-1186)

[1186](#)

**AUTORES / AUTHORS:** - Shames DS; Elkins K; Walter K; Holcomb T; Du P; Mohl D; Xiao Y; Pham T; Haverty PM; Liederer B; Liang X; Yauch RL; O'Brien T; Bourgon R; Koeppen H; Belmont LD

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliation: Genentech, Inc., South San Francisco, California.

**RESUMEN / SUMMARY:** - PURPOSE: We sought to identify predictive biomarkers for a novel nicotinamide phosphoribosyltransferase (NAMPT) inhibitor. EXPERIMENTAL DESIGN: We use a NAMPT inhibitor, GNE-617, to evaluate nicotinic acid rescue status in a panel of more than 400 cancer cell lines. Using correlative analysis and RNA interference (RNAi), we identify a specific biomarker for nicotinic acid rescue status. We next determine the mechanism of regulation of expression of the biomarker. Finally, we develop immunohistochemical (IHC) and DNA methylation assays and evaluate cancer tissue for prevalence of the biomarker across indications. RESULTS: Nicotinate phosphoribosyltransferase (NAPRT1) is necessary for nicotinic acid rescue and its expression is the major determinant of rescue status. We demonstrate that NAPRT1 promoter methylation accounts for NAPRT1 deficiency in cancer cells, and NAPRT1 methylation is predictive of rescue status in cancer cell lines. Bisulfite next-generation sequencing mapping of the NAPRT1 promoter identified tumor-specific sites of NAPRT1 DNA methylation and enabled the development of a quantitative methylation-specific PCR (QMSP) assay suitable for use on archival formalin-fixed paraffin-embedded tumor tissue. CONCLUSIONS: Tumor-specific promoter hypermethylation of NAPRT1 inactivates one of two NAD salvage pathways, resulting in synthetic lethality with the coadministration of a NAMPT inhibitor. NAPRT1 expression is lost due to promoter hypermethylation in most cancer types evaluated at frequencies ranging from 5% to 65%. NAPRT1-specific immunohistochemical or DNA methylation assays can be used on archival formalin paraffin-embedded cancer tissue to identify patients likely to benefit from coadministration of a Nampt inhibitor and nicotinic acid. Clin Cancer Res; 1-12. ©2013 AACR.

[389]

**TÍTULO / TITLE:** - Phenethyl Isothiocyanate Inhibits Proliferation and Induces Apoptosis in Pancreatic Cancer Cells In Vitro and in a MIAPaca2 Xenograft Animal Model.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.795979](#)

**AUTORES / AUTHORS:** - Stan SD; Singh SV; Whitcomb DC; Brand RE

**INSTITUCIÓN / INSTITUTION:** - a Department of Nutrition Science , Purdue University , West Lafayette , Indiana , USA.

**RESUMEN / SUMMARY:** - Pancreatic cancer is often diagnosed at an advanced stage and it has a poor prognosis that points to an increased need to develop effective chemoprevention strategies for this disease. We examined the ability of phenethyl isothiocyanate (PEITC), a naturally occurring isothiocyanate found in cruciferous vegetables, to inhibit the growth of pancreatic cancer cells in vitro and in a MIAPaca2 xenograft animal model. Exposure to PEITC inhibited pancreatic cancer cell growth in a dose-dependent manner, with an IC50 of approximately 7 μmol/L. PEITC treatment induced G2/M phase cell cycle arrest, downregulated the antiapoptotic proteins Bcl-2 and Bcl-XL, upregulated the proapoptotic protein Bak, and suppressed Notch 1 and 2 levels. In addition, treatment with PEITC induced cleavage of poly-(ADP-ribose) polymerase and led to increased cytoplasmic histone-associated DNA fragmentation and subdiploid (apoptotic) fraction in pancreatic cancer cells. Oral administration of PEITC suppressed the growth of pancreatic cancer cells in a MIAPaca2 xenograft

animal model. Our data show that PEITC exerts its inhibitory effect on pancreatic cancer cells through several mechanisms, including G2/M phase cell cycle arrest and induction of apoptosis, and supports further investigation of PEITC as a chemopreventive agent for pancreatic cancer.

[390]

**TÍTULO / TITLE:** - Tumor Necrosis Factor-Related Apoptosis Inducing Ligand Gene Polymorphisms are Correlated with Gastric Cancer in Central China.

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

**REVISTA / JOURNAL:** - Pharm Res. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1007/s11095-013-1217-y](#)

**AUTORES / AUTHORS:** - Wang C; Xu S; Yi F; Wang X; Lei Y; Huang S; Zhou R; Xia B

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Zhongnan Hospital of Wuhan, University School of Medicine, Donghu Road 169, Wuhan, 430071, Hubei Province, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: To investigate the association of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) gene polymorphisms with gastric cancer in Chinese Han population in central China. METHODS: A total of 304 patients with gastric cancer confirmed by histopathology and 421 unrelated healthy controls were studied. Gene polymorphisms of TRAIL (G1525A and C1595T) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. RESULTS: The frequency of the genotype carriers of TRAIL 1525A (GA + AA) and 1595T (CT + TT) was significantly lower in gastric cancer than in healthy controls (37.2% vs. 61.5%,  $P < 0.001$ , OR = 0.581, 95% CI 0.442 ~ 0.764; 36.2% vs. 62.0%,  $P < 0.001$ , OR = 0.570, 95% CI 0.433 ~ 0.750, respectively). Stratification analysis showed that both TRAIL 1525A (GA + AA) and 1595T (CT + TT) carriers were associated with poorly-differentiated gastric cancer compared to 1525GG genotype and 1595CC genotype (OR = 0.516, 95%CI 0.279 ~ 0.957,  $P = 0.026$ ; OR = 0.395, 95%CI 0.207 ~ 0.753,  $P = 0.004$ , respectively). CONCLUSIONS: TRAIL G1525A and C1595T gene polymorphisms were significantly correlated with the susceptibility to gastric cancer in Chinese Han population in central China.

[391]

**TÍTULO / TITLE:** - Chemotherapy stimulates syndecan-1 shedding: A potentially negative effect of treatment that may promote tumor relapse.

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

**REVISTA / JOURNAL:** - Matrix Biol. 2013 Oct 18. pii: S0945-053X(13)00134-0. doi: 10.1016/j.matbio.2013.10.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.matbio.2013.10.005](#)

**AUTORES / AUTHORS:** - Ramani VC; Sanderson RD

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

**RESUMEN / SUMMARY:** - In patients with multiple myeloma, the heparan sulfate proteoglycan syndecan-1 (CD138) is shed from the surface of tumor cells and accumulates in the serum and within the extracellular matrix of the bone marrow where it promotes tumor growth and metastasis. In the present study we discovered

that commonly used anti-myeloma drugs stimulate syndecan-1 shedding both in vitro and in animals bearing myeloma tumors. Enhanced shedding is accompanied by increased syndecan-1 synthesis prior to drug induced tumor cell death. Addition of a caspase inhibitor blocks the drug-induced shedding of syndecan-1 in vitro indicating that shedding is linked to the onset of apoptosis. ADAM inhibitors or siRNA targeting ADAMs blocked drug-induced shedding suggesting that upregulation or activation of ADAMs is responsible for cleaving syndecan-1 from the tumor cell surface. These results reveal that myeloma chemotherapy stimulates synthesis and shedding of syndecan-1, a potentially negative side effect that may lead to the accumulation of high levels of syndecan-1 to establish a microenvironment that nurtures relapse and promotes tumor progression. Interestingly, we also found that chemotherapeutic drugs stimulated syndecan-1 shedding from pancreatic cancer cells as well, indicating that drug-induced shedding of syndecan-1 may occur in many cancer types. Overall, our results indicate that the use of metalloproteinase inhibitors (to inhibit syndecan-1 shedding) in combination with chemotherapy may represent a novel therapeutic strategy to prevent re-establishment of a microenvironment conducive for tumor relapse.

[392]

**TÍTULO / TITLE:** - Bortezomib-induced apoptosis in cultured pancreatic cancer cells is associated with ceramide production.

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

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

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2318-3](#)

**AUTORES / AUTHORS:** - Gong L; Yang B; Xu M; Cheng B; Tang X; Zheng P; Jing Y; Wu GJ

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Wuxi No. 2 People's Hospital, Wuxi, Jiangsu, China.

**RESUMEN / SUMMARY:** - **PURPOSE:** The proteasome inhibitor bortezomib (PS-341) has displayed significant efficiency against pancreatic cancer cells. However, the underlying mechanisms are not fully understood. Here, we tested if ceramide production was involved in the bortezomib's effect. **METHODS:** Two transformed pancreatic cancer cell lines (PANC-1 and Mia) and the primary pancreatic cancer cells were used. Cell death was analyzed by MTT viability assay and trypan blue staining. Cell apoptosis was analyzed by Histone DNA-ELISA assay and Annexin V FACS. Western blots were used to test signal protein changes. The cellular ceramide level after bortezomib treatment was also determined. **RESULTS:** In cultured pancreatic cancer cells, bortezomib increased cellular ceramide production to promote cell apoptosis. The ceramide de novo synthase inhibitor fumonisin B1 (F-B1) suppressed bortezomib-induced ceramide production and apoptosis, while exogenously added C6-ceramide facilitated bortezomib-induced pancreatic cancer cell death. Meanwhile, 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), the inhibitor of glucosylceramide synthetase as well as the sphingosine kinase 1 inhibitors (SKI-II and SKI-IV), facilitated bortezomib-induced ceramide production and subsequent cell apoptosis. Further, bortezomib-induced pro-apoptotic c-Jun N-terminal kinase (JNK) activation was also associated with ceramide production. JNK activation by bortezomib was suppressed by F-B1, but was enhanced by SKI-II and PDMP in pancreatic cancer

cells. Finally, C6-ceramide, SKI-II, and PDMP dramatically enhanced bortezomib-induced cytotoxicity in primary cultured pancreatic cancer cells. CONCLUSIONS: We found that bortezomib-induced apoptosis was associated with ceramide production in primary and transformed pancreatic cancer cells.

[393]

**TÍTULO / TITLE:** - Magnolol induces apoptosis in MCF-7 human breast cancer cells through G2/M phase arrest and caspase-independent pathway.

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

**REVISTA / JOURNAL:** - Pharmazie. 2013 Sep;68(9):755-62.

**AUTORES / AUTHORS:** - Zhou Y; Bi Y; Yang C; Yang J; Jiang Y; Meng F; Yu B; Khan M; Ma T; Yang H

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, Liaoning Provincial Key Laboratory of Biotechnology and Drug Discovery, Liaoning Normal University, Dalian, China.

**RESUMEN / SUMMARY:** - Magnolol, a small-molecule hydroxylated biphenol, isolated from the root and stem bark of *Magnolia officinalis*, has been shown to possess antiproliferative effect on various cancer cell lines. In the current study, we found that magnolol potently inhibited proliferation and induced apoptosis in MCF-7 human breast cancer cells. Further mechanistic studies revealed that induction of apoptosis is associated with cell cycle arrest at G2/M phase, increased generation of reactive oxygen species (ROS), reduced mitochondrial membrane potential (MMP), release of cytochrome c (Cyto c) and apoptosis inducing factor (AIF) from mitochondria to cytosol, upregulation of Bax, p21 and p53, and down-regulation of Bcl-2, cyclin B1 and cyclin-dependent kinase 1 (CDK1). Our findings indicated that magnolol induced apoptosis in MCF-7 cells via the intrinsic pathway with release of AIF from mitochondrial and G2/M phase arrest pathway. Therefore, magnolol might be a potential lead compound in the therapy of breast cancer.

[394]

**TÍTULO / TITLE:** - Effects of single nucleotide polymorphisms of FMO3 and FMO6 genes on pharmacokinetic characteristics of sulindac sulfide in premature labor.

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

**REVISTA / JOURNAL:** - Drug Metab Dispos. 2013 Oct 30.

●● [Enlace al texto completo \(gratis o de pago\) 1124/dmd.113.054106](#)

**AUTORES / AUTHORS:** - Park S; Lee NR; Lee KE; Park JY; Kim YJ; Gwak HS

**INSTITUCIÓN / INSTITUTION:** - Ewha Womans University;

**RESUMEN / SUMMARY:** - This study aimed to investigate the effects of polymorphisms of FMO3 and FMO6 genes on the pharmacokinetics of sulindac sulfide, the active metabolite of sulindac, in patients with preterm labors. Ten single nucleotide polymorphisms (SNPs) were genotyped, and plasma sulindac sulfide concentrations were measured at 0, 1.5, 4, and 10 hr after drug administration. The area under the curve from time 0 to the last sampling time point (AUClast) for sulindac sulfide was obtained. The AUClast of sulindac sulfide was significantly higher in patients with variant-type homozygotes of FMO3 (rs909530) than those with ancestral alleles or heterozygotes. FMO3 (rs2266780) was in complete linkage disequilibrium with FMO6

(rs7885012), and there was a marginal significance between genotypes ( $P = 0.049$ ). From multiple linear regression models, FMO3 (rs909530) was found to have significant influence on the AUClast of sulindac sulfide after adjusting for gestational age, weight, and all studied SNPs. The predictive contribution of rs909530 to variability of sulindac sulfide AUClast was 27.0 %. In conclusion, the results of this study could help clinicians predict efficacies and side effects of sulindac for developing individualized treatment for patients with preterm labors.

[395]

**TÍTULO / TITLE:** - Impact of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and MGMT expression on dacarbazine resistance of Hodgkin's lymphoma cells.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Nov 13. pii: S0145-2126(13)00389-5. doi: 10.1016/j.leukres.2013.11.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.11.001](#)

**AUTORES / AUTHORS:** - Kewitz S; Stiefel M; Kramm CM; Staeger MS

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, Martin-Luther-University Halle-Wittenberg, Halle, Germany.

**RESUMEN / SUMMARY:** - We analyzed the methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter and mRNA expression in HL cells and assessed the response of these cells to dacarbazine. Expression of MGMT correlated with the presence of non-methylated promoters and cell lines with non-methylated promoters showed increased resistance against dacarbazine. KM-H2 cells expressed fusion transcripts between MGMT and proline-rich coiled-coil 2B (PRRC2B) but no wild type MGMT transcripts. Dacarbazine sensitivity suggested that fusion transcripts are translated into a protein with reduced functionality. MGMT promoter methylation predicts dacarbazine sensitivity of HL cells and it might be interesting to analyze this factor in HL patients.

[396]

**TÍTULO / TITLE:** - Systematic expression analysis of genes related to multidrug-resistance in isogenic docetaxel- and adriamycin-resistant breast cancer cell lines.

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

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 Sep 29.

●● Enlace al texto completo (gratis o de pago) [1007/s11033-013-2725-x](#)

**AUTORES / AUTHORS:** - Li WJ; Zhong SL; Wu YJ; Xu WD; Xu JJ; Tang JH; Zhao JH

**INSTITUCIÓN / INSTITUTION:** - Suzhou Municipal Hospital affiliated to Nanjing Medical University, Suzhou, 215002, China.

**RESUMEN / SUMMARY:** - Docetaxel (Doc) and adriamycin (Adr) are two of the most effective chemotherapeutic agents in the treatment of breast cancer. However, their efficacy is often limited by the emergence of multidrug resistance (MDR). The purpose of this study was to investigate MDR mechanisms through analyzing systematically the expression changes of genes related to MDR in the induction process of isogenic drug resistant MCF-7 cell lines. Isogenic resistant sublines selected at 100 and 200 nM Doc (MCF-7/100 nM Doc and MCF-7/200 nM Doc) or at 500 and 1,500 nM Adr (MCF-

7/500 nM Adr and MCF-7/1,500 nM) were developed from human breast cancer parental cell line MCF-7, by exposing MCF-7 to gradually increasing concentrations of Doc or Adr in vitro. Cell growth curve, flow cytometry and MTT cytotoxicity assay were performed to evaluate the MDR characteristics developed in the sublines. Some key genes on the pathways related to drug resistance (including drug-transporters: MDR1, MRP1 and BCRP; drug metabolizing-enzymes: CYP3A4 and glutathione S-transferases (GST) pi; target genes: topoisomerase II (TopoIIalpha) and Tubb3; apoptosis genes: Bcl-2 and Bax) were analyzed at RNA and protein expression levels by real time RT-qPCR and western blot, respectively. Compared to MCF-7/S (30.6 h), cell doubling time of MCF-7/Doc (41.6 h) and MCF-7/Adr (33.8 h) were both prolonged, and the cell proportion of resistant sublines in G1/G2 phase increased while that in S-phase decreased. MCF-7/100 nM Doc and MCF-7/200 nM Doc was 22- and 37-fold resistant to Doc, 18- and 32-fold to Adr, respectively. MCF-7/500 nM Adr and MCF-7/1,500 nM Adr was 61- and 274-fold resistant to Adr, three and 12-fold to Doc, respectively. Meantime, they also showed cross-resistance to the other anticancer drugs in different degrees. Compared to MCF-7/S, RT-qPCR and Western blot results revealed that the expression of MDR1, MRP1, BCRP, Tubb3 and Bcl-2 were elevated in both MCF-7/Doc and MCF-7/Adr, and TopoIIalpha, Bax were down-regulated in both the sublines, while CYP3A4, GST pi were increased only in MCF-7/Doc and MCF-7/Adr respectively. Furthermore, the changes above were dose-dependent. The established MCF-7/Doc or MCF-7/Adr has the typical MDR characteristics, which can be used as the models for resistance mechanism study. The acquired process of MCF-7/S resistance to Doc or Adr is gradual, and is complicated with the various pathways involved in. There are some common resistant mechanisms as well as own drug-specific changes between both the sublines.

[397]

**TÍTULO / TITLE:** - Proteomic Markers of DNA Repair and PI3K Pathway Activation Predict Response to the PARP Inhibitor BMN 673 in Small Cell Lung Cancer.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 15;19(22):6322-8. doi: 10.1158/1078-0432.CCR-13-1975. Epub 2013 Sep 27.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-1975](#)

**AUTORES / AUTHORS:** - Cardnell RJ; Feng Y; Diao L; Fan YH; Masrourpour F; Wang J; Shen Y; Mills GB; Minna JD; Heymach JV; Byers LA

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Department of Thoracic/Head and Neck Medical Oncology; Bioinformatics and Computational Biology; Systems Biology, UT MD Anderson Cancer Center, Houston; Hamon Center for Therapeutic Oncology Research and the Simmons Comprehensive Cancer Center, UT Southwestern, Dallas, Texas; and Biomarin Pharmaceuticals Inc., Novato, California.

**RESUMEN / SUMMARY:** - PURPOSE: Small cell lung carcinoma (SCLC) is an aggressive malignancy affecting nearly 30,000 people annually in the United States. We have previously identified elevated PARP1 levels in SCLC and demonstrated in vitro sensitivity to the PARP inhibitors AZD 2281 and AG014699. Here, we evaluate activity of a novel, potent PARP inhibitor, BMN 673, and identify markers of response as a basis for developing predictive markers for clinical application. EXPERIMENTAL

DESIGN: Inhibition of SCLC proliferation by BMN 673 was assayed in vitro and effects on tumor growth were measured in SCLC xenograft models. Protein expression and pathway activation was assessed by reverse phase protein array and western blot analysis. PARP inhibition was confirmed using a PAR ELISA. RESULTS: We demonstrate striking, single agent activity of BMN 673 in SCLC cell lines and xenografts, with single agent BMN 673 exhibiting in vivo activity similar to cisplatin. Sensitivity to BMN 673 was associated with elevated baseline expression levels of several DNA repair proteins, whereas greater drug resistance was observed in SCLC models with baseline activation of the PI3K/mTOR pathway. Furthermore, we developed and confirmed these data with a novel "DNA repair score" consisting of a group of 17 DNA repair proteins. CONCLUSIONS: Elevated expression of multiple DNA repair proteins, as well as a corresponding "DNA repair protein score," predict response to BMN 673 in in vitro SCLC models. These observations complement recent work in which PI3K inhibition sensitizes breast cancer models to PARP inhibition, suggesting cooperation between DNA repair and PI3K pathways. Clin Cancer Res; 19(22); 6322-8. ©2013 AACR.

[398]

**TÍTULO / TITLE:** - Targeting Small Cell Lung Cancer Harboring PIK3CA Mutation with a Selective Oral PI3K Inhibitor PF-4989216.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 15.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-1663](#)

**AUTORES / AUTHORS:** - Walls M; Baxi SM; Mehta PP; Liu KK; Zhu J; Estrella H; Li C; Zientek M; Zong Q; Smeal T; Yin MJ

**INSTITUCIÓN / INSTITUTION:** - Research, Pfizer Inc.

**RESUMEN / SUMMARY:** - PURPOSE: Constitutive activation of PI3K occurs frequently in many human tumors via either gene mutation in the p110alpha catalytic subunit of PI3K or functional loss of tumor suppressor PTEN. Small cell lung cancer (SCLC) patients have very poor prognosis and survival rates such that an effective targeted therapy is in strong demand for these patients. In this study, we characterized the highly selective oral PI3K inhibitor, PF-4989216, in preclinical SCLC models to investigate whether targeting the PI3K pathway is an effective targeted therapy option for SCLCs that harbor a PIK3CA mutation. EXPERIMENTAL DESIGN: A panel of SCLC lines with PIK3CA mutation or PTEN loss were treated with PF-4989216 in several in vitro assays including: PI3K pathway signaling, cell viability, apoptosis, cell cycle progression, and cell transformation. SCLC lines that were sensitive in vitro to PF-4989216 were further evaluated by in vivo animal studies to determine the pharmacokinetic/pharmacodynamic relationship and tumor growth inhibition by PF-4989216 treatment. RESULTS: PF-4989216 inhibited PI3K downstream signaling and subsequently led to apoptosis induction, and inhibition in cell viability, transformation, and xenograft tumor growth in SCLCs harboring PIK3CA mutation. In SCLCs with PTEN loss, PF-4989216 also inhibited PI3K signaling but did not induce BIM-mediated apoptosis nor was there any effect in cell viability or transformation. These results implicate differential tumorigenesis and apoptosis mechanisms in SCLCs harboring PIK3CA mutation versus PTEN loss. CONCLUSION: Our results suggest that PF-

4989216 is a potential cancer drug candidate for SCLC patients with PIK3CA mutation but not PTEN loss.

[399]

**TÍTULO / TITLE:** - The chemokine system, and its CCR5 and CXCR4 receptors, as potential targets for personalized therapy in cancer.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Oct 18. pii: S0304-3835(13)00735-0. doi: 10.1016/j.canlet.2013.10.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.10.006](#)

**AUTORES / AUTHORS:** - Weitzenfeld P; Ben-Baruch A

**INSTITUCIÓN / INSTITUTION:** - Dept. Cell Research and Immunology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel.

**RESUMEN / SUMMARY:** - Chemokines and their receptors regulate the trafficking of leukocytes in hematopoiesis and inflammation, and thus are fundamental to the immune integrity of the host. In parallel, members of the chemokine system exert a large variety of functions that dictate processes of cancer development and progression. Chemokines can act as pro-tumoral or anti-tumoral regulators of malignancy by affecting cells of the tumor microenvironment (leukocytes, endothelial cells, fibroblasts) and the tumor cells themselves (migration, invasion, proliferation, resistance to chemotherapy). Several of the chemokines are generally skewed towards the cancer-promoting direction, including primarily the CCR5-CCL5 (RANTES) and the CXCR4-CXCL12 (SDF-1) axes. This review provides a general view of chemokines and chemokine receptors as regulators of malignancy, describing their multi-faceted activities in cancer. The tumor-promoting activities of the CCR5-CCL5 and CXCR4-CXCL12 pathways are enlightened, emphasizing their potential use as targets for personalized therapy. Indeed, novel blockers of chemokines and their receptors are constantly emerging, and two chemokine receptor inhibitors were recently approved for clinical use: Maraviroc for CCR5 and Plerixafor for CXCR4. The review addresses ongoing pre-clinical and clinical trials using these modalities and others in cancer. Then, challenges and opportunities of personalized therapy directed against chemokines and their receptors in malignancy are discussed, demonstrating that such novel personalized cancer therapies hold many challenges, but also offer hope for cancer patients.

[400]

**TÍTULO / TITLE:** - G15, a GPR30 antagonist, induces apoptosis and autophagy in human oral squamous carcinoma cells.

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

**REVISTA / JOURNAL:** - Chem Biol Interact. 2013 Nov 25;206(2):375-84. doi: 10.1016/j.cbi.2013.10.014. Epub 2013 Oct 23.

●● Enlace al texto completo (gratis o de pago) [1016/j.cbi.2013.10.014](#)

**AUTORES / AUTHORS:** - Bai LY; Weng JR; Hu JL; Wang D; Sargeant AM; Chiu CF

**INSTITUCIÓN / INSTITUTION:** - College of Medicine, China Medical University, Taichung 40402, Taiwan; Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taichung 40447, Taiwan.

**RESUMEN / SUMMARY:** - As GPR30 has been implicated in mediating cancer cell proliferation, this study aimed to examine the antitumor effect of the GPR30 antagonist G15 in human oral squamous cell carcinoma (OSCC). G15 induced dose-dependent cytotoxicity, apoptosis and G2/M cell cycle arrest in a panel of OSCC cells. The results showed that G15 could inhibit the growth of the oral cancer cells with IC50 value 11.2µM for SCC4, 15.6µM for SCC9, and 7.8µM for HSC-3, respectively. Flow cytometric analysis and Comet assay indicated that G15 suppressed the viability of SCC4 and HSC-3 cells by inducing apoptosis and G2/M arrest. In addition, G15 down regulated the expression of Akt, cell cycle-related proteins, and mitogen-activated protein kinases, but increased the levels of LC3B-II and the accumulation of autophagosomes. Inhibition of autophagy by chloroquine does not affect the G15-induced apoptosis in SCC4 cells. Mechanistic evidence indicated that the antiproliferative effect was mediated through the downregulation of cdc2, cdc25c and NF-kappaB expression. Taken together, our findings suggest the potential of G15 in treating OSCC.

[401]

**TÍTULO / TITLE:** - Gallic acid induces apoptosis and inhibits cell migration by upregulating miR-518b in SW1353 human chondrosarcoma cells.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):91-8. doi: 10.3892/ijo.2013.2155. Epub 2013 Oct 30.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2155](#)

**AUTORES / AUTHORS:** - Liang W; Li X; Li Y; Li C; Gao B; Gan H; Li S; Shen J; Kang J; Ding S; Lin X; Liao L

**INSTITUCIÓN / INSTITUTION:** - Research Base of Traditional Chinese Medicine Syndrome, Fujian University of Traditional Chinese Medicine, Fuzhou 350122, P.R. China.

**RESUMEN / SUMMARY:** - Gallic acid (GA), a natural agent, is widely distributed in plants with a range of biological effects and has been of potential interest as anticancer agent. However, its effects on chondrosarcoma cell apoptosis are still undefined. In the present study, the possible mechanisms of GA-induced apoptosis were explored in SW1353 cells, a human chondrosarcoma cell line. Our results showed that GA inhibited cell viability dose- and time-dependently. Morphological examination of GA-treated cells exhibited the typical features of cell death, such as rounding up of the cells and cell shrinkage. Wound-healing assay indicated that GA inhibited the migratory abilities of SW1353 cells. Hoechst 33258 staining assay and Annexin V/PI staining assay exhibited apoptosis induction by GA. To determine the molecular mechanism of GA-induced apoptosis, the expression levels Bcl-2, Bax, caspase-3 and caspase-9 were determined in SW1353 cells treated with GA. We found that GA downregulated the expression of the anti-apoptotic protein Bcl-2, and upregulated the expression of the pro-apoptotic protein Bax, and the activation of caspase-3 and caspase-9. To identify the possible mechanisms, the changes of microRNA expression were tested using the miRCURY LNA expression array. It was observed that the miR-518b gene was upregulated in treated cells. Taken together, these data show that GA induces apoptosis and inhibits cell migration by upregulating miR-518b in SW1353 cells.

[402]

**TÍTULO / TITLE:** - PX-12 inhibits the growth of A549 lung cancer cells via G2/M phase arrest and ROS-dependent apoptosis.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):301-8. doi: 10.3892/ijo.2013.2152. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2152](#)

**AUTORES / AUTHORS:** - You BR; Shin HR; Park WH

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju 561-180, Republic of Korea.

**RESUMEN / SUMMARY:** - PX-12 (1-methylpropyl 2-imidazolyl disulfide) is an inhibitor of thioredoxin (Trx-1), which has antitumor effects. However, little is known about the toxicological effect of PX-12 on cancer cells. We investigated the anti-growth effects of PX-12 on A549 lung cancer cells in relation to reactive oxygen species (ROS) and glutathione (GSH) levels. Based on MTT assays, PX-12 inhibited the growth of A549 cells with an IC50 of approximately 20 microM at 72 h. DNA flow cytometric analysis indicated that PX-12 significantly induced the G2/M phase arrest of the cell cycle in A549 cells. This agent also induced apoptotic cell death, as demonstrated by Annexin V-FITC staining cells and the loss of mitochondrial membrane potential MMP (psim). In addition, the administration of Bax siRNA attenuated PX-12-induced A549 cell death. All the tested caspase inhibitors, especially Z-VAD significantly prevented apoptosis induced by PX-12. With respect to ROS and GSH levels, PX-12 increased ROS levels including O2\*- in A549 cells and induced GSH depletion. N-acetyl cysteine (NAC) markedly reduced ROS levels in PX-12-treated A549 cells. NAC also prevented apoptotic cell death and GSH depletion induced by PX-12. This is the first report to show that PX-12 inhibits the growth of A549 cells via G2/M phase arrest, and Bax-mediated and ROS-dependent apoptosis.

[403]

**TÍTULO / TITLE:** - DPMA, a deoxypodophyllotoxin derivative, induces apoptosis and anti-angiogenesis in non-small cell lung cancer A549 cells.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Dec 15;23(24):6650-5. doi: 10.1016/j.bmcl.2013.10.048. Epub 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.10.048](#)

**AUTORES / AUTHORS:** - Sang CY; Xu XH; Qin WW; Liu JF; Hui L; Chen SW

**INSTITUCIÓN / INSTITUTION:** - School of Pharmacy, Lanzhou University, Lanzhou 730000, PR China.

**RESUMEN / SUMMARY:** - We found that the deoxypodophyllotoxin derivative, 2,6-dimethoxy-4-(6-oxo-(5R,5aR,6,8,8aR,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl)phenyl (@-1-amino-4-(methylthio)-1-oxobutan-2-yl)carbamate (DPMA), exhibited superior cytotoxicity compared with etoposide. In this study, we investigated the mechanism of action of DPMA. DPMA exhibited anti-proliferative activity and induced apoptosis in A549 cells in a dose- and time-dependant manner. DPMA

inhibited microtubule formation and induced expression of Bax, cleaved caspase-3, p53 and ROS, and inhibited Bcl-2 expression. DPMA also affected cyclinB1, cdc2 and p-cdc2 expression, inducing cell cycle arrest. DPMA also inhibited tube formation of VEGF-induced human umbilical vein endothelial cells. These studies demonstrate that DPMA inhibits p53/cdc2/Bax signaling, thereby inhibiting cell growth/angiogenesis and inducing apoptosis.

[404]

**TÍTULO / TITLE:** - A novel hydroxamic acid derivative, MHY218, induces apoptosis and cell cycle arrest through downregulation of NF-kappaB in HCT116 human colon cancer cells.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):256-64. doi: 10.3892/ijo.2013.2163. Epub 2013 Nov 1.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.2163](#)

**AUTORES / AUTHORS:** - Kim MK; Kang YJ; Kim DH; Hossain MA; Jang JY; Lee SH; Yoon JH; Chun P; Moon HR; Kim HS; Chung HY; Kim ND

**INSTITUCIÓN / INSTITUTION:** - Division of Pharmacy, College of Pharmacy, Molecular Inflammation Research Center for Aging Intervention (MRCA), Pusan National University, Busan 609-735, Republic of Korea.

**RESUMEN / SUMMARY:** - Colorectal cancer (CRC) is one of the most common malignant diseases and frequent cause of cancer deaths in the world. In spite of the significant advances in conventional therapeutic approaches to CRC, most patients ultimately die of their disease. There is a need to develop novel preventive approaches for this malignancy. This study was carried out to investigate the anticancer effect of MHY218, a hydroxamic acid derivative, in HCT116 human colon cancer cells. Treatment of cells with MHY218 resulted in growth inhibition and induction of apoptosis in a concentration-dependent manner. MHY218 induced G2/M phase arrest in the cell cycle progression which was observed by flow cytometry analysis, and a decrease in the protein expression of cyclin B1 and its activating partners Cdc25C and Cdc2. MHY218 also caused an increase in the expression levels of p21WAF1/CIP1, a G2/M phase inhibitor, in a p53-independent pathway. The induction of apoptosis was observed by decreased viability, DNA fragmentation, cleavage of poly(ADP-ribose) polymerase, alteration in the ratio of Bax/Bcl-2 protein expression, and activation of caspase-3, -8 and -9. In addition, MHY218 treatment showed downregulation of the expression levels of the transcription factor nuclear factor-kappa B (NF-kappaB) in the nucleus, which has been reported to be implicated in the apoptotic cell death of several types of cancer cells, suppression of TNF-alpha-induced NF-kappaB activation, inhibition of cyclooxygenase-2 expression, repression of matrix metalloproteinase-9 activation and decrease of 5-lipoxygenase in a concentration-dependent manner. These results suggest that MHY218 may be a useful candidate to be used in the chemoprevention and/or treatment of colon cancer.

[405]

**TÍTULO / TITLE:** - Oleifolioside B-mediated autophagy promotes apoptosis in A549 human non-small cell lung cancer cells.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):1943-50. doi: 10.3892/ijo.2013.2143. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2143](#)

**AUTORES / AUTHORS:** - Jin CY; Yu HY; Park C; Han MH; Hong SH; Kim KS; Lee YC; Chang YC; Cheong J; Moon SK; Kim GY; Moon HI; Kim WJ; Lee JH; Choi YH

**INSTITUCIÓN / INSTITUTION:** - School of Pharmaceutical Science, Zhengzhou University, Henan 450001, P.R. China.

**RESUMEN / SUMMARY:** - The biochemical mechanisms of cell death by oleifolioside B (OB), a cycloartane-type triterpene glycoside isolated from *Dendropanax morbifera* Leveille, were investigated in A549 human lung carcinoma cells. Our data indicated that exposure to OB led to caspase activation and typical features of apoptosis; however, apoptotic cell death was not prevented by z-VAD-fmk, a pan-caspase inhibitor, demonstrating that OB-induced apoptosis was independent of caspase activation. Subsequently, we found that OB increased autophagy, as indicated by an increase in monodansylcadaverine fluorescent dye-labeled autophagosome formation and in the levels of the autophagic form of microtubule-associated protein 1 light chain 3 and Atg3, an autophagy-specific gene, which is associated with inhibiting phospho-nuclear factor erythroid 2-related factor 2 (Nrf2) expression. However, pretreatment with bafilomycin A1, an autophagy inhibitor, attenuated OB-induced apoptosis and dephosphorylation of Nrf2. The data suggest that OB-induced autophagy functions as a death mechanism in A549 cells and OB has potential as a novel anticancer agent capable of targeting apoptotic and autophagic cell death and the Nrf2 signaling pathway.

[406]

**TÍTULO / TITLE:** - Tumor-Targeting with Novel Non-Benzoyl 6-Substituted Straight Chain Pyrrolo[2,3-d]pyrimidine Antifolates via Cellular Uptake by Folate Receptor alpha and Inhibition of de Novo Purine Nucleotide Biosynthesis.

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

**REVISTA / JOURNAL:** - J Med Chem. 2013 Oct 30.

●● Enlace al texto completo (gratis o de pago) [1021/jm401139z](#)

**AUTORES / AUTHORS:** - Wang Y; Cherian C; Orr S; Mitchell-Ryan S; Hou Z; Raghavan S; Matherly LH; Gangjee A

**INSTITUCIÓN / INSTITUTION:** - Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, Pennsylvania 15282, United States.

**RESUMEN / SUMMARY:** - A new series of 6-substituted straight side chain pyrrolo[2,3-d]pyrimidines 3a-d with varying chain lengths (n = 5-8) was designed and synthesized as part of our program to provide targeted antitumor agents with folate receptor (FR) cellular uptake specificity and glycinamide ribonucleotide formyltransferase (GARFTase) inhibition. Carboxylic acids 4a-d were converted to the acid chlorides and reacted with diazomethane, followed by 48% HBr to generate the alpha-bromomethylketones 5a-d. Condensation of 2,4-diamino-6-hydroxypyrimidine 6 with 5a-d afforded the 6-substituted pyrrolo[2,3-d]pyrimidines 7a-d. Hydrolysis and subsequent coupling with diethyl L-glutamate and saponification afforded target compounds 3a-d. Compounds 3b-d showed selective cellular uptake via FRalpha and -

beta, associated with high affinity binding and inhibition of de novo purine nucleotide biosynthesis via GARFTase, resulting in potent inhibition against FR-expressing Chinese hamster cells and human KB tumor cells in culture. Our studies establish, for the first time, that a side chain benzoyl group is not essential for tumor-selective drug uptake by FRalpha.

[407]

**TÍTULO / TITLE:** - Bioreductive activation of mitoxantrone by NADPH cytochrome P450 reductase does not change its apoptotic stimuli properties in regard to sensitive and multidrug resistant leukaemia HL60 cells.

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

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 Dec 5;721(1-3):141-50. doi: 10.1016/j.ejphar.2013.09.041. Epub 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejphar.2013.09.041](#)

**AUTORES / AUTHORS:** - Kostrzewa-Nowak D; Tarasiuk J

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, University of Szczecin, 3c Felczaka Street, 71-412 Szczecin, Poland.

**RESUMEN / SUMMARY:** - The objective of this study was to examine the effect of bioreductive activation of antitumour drug, mitoxantrone (MX), by liver NADPH cytochrome P450 reductase (CPR) on inducing apoptosis of human promyelocytic sensitive leukaemia HL60 cell line and its multidrug resistance (MDR) sublines exhibiting two different phenotypes of MDR related to the overexpression of P-glycoprotein (HL60/VINC) or MRP1 (HL60/DOX). It was found that non-activated as well as CPR-activated form of MX used at IC90 were able to influence cell cycle of sensitive HL60 as well as resistant cells and induce apoptosis. Interestingly, it was evidenced that HL60/VINC cells were more susceptible to undergo caspase-3/caspase-8-dependent apoptosis induced by both studied forms of MX compared to HL60 and HL60/DOX cells. However, the examined agent did not change the expression of Fas receptors on the surface of HL60 sensitive as well as resistant cells regardless of its form used in the study. Obtained results suggest that CPR-dependent reductive activation of MX does not change its apoptotic stimuli properties in regard to sensitive HL60 and multidrug resistant (HL60/VINC and HL60/DOX) leukaemia cells. Nevertheless, taking into account that side toxic effects observed in course of patient treatment with antitumour drugs are dose-dependent, it seems that the reported increase in antiproliferative activity and ability to induce apoptosis of MX after its reductive activation by exogenous CPR against the MDR cells overexpressing both P-glycoprotein and MRP1 at much more lower concentrations of this drug could be of clinical importance for the treatment of tumours resistant to classical chemotherapy.

[408]

**TÍTULO / TITLE:** - YM155 sensitizes ovarian cancer cells to cisplatin inducing apoptosis and tumor regression.

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

**REVISTA / JOURNAL:** - Gynecol Oncol. 2013 Nov 19. pii: S0090-8258(13)01335-8. doi: 10.1016/j.ygyno.2013.11.013.

●● Enlace al texto completo (gratis o de pago) [1016/j.ygyno.2013.11.013](#)

**AUTORES / AUTHORS:** - Mir R; Stanzani E; Martinez-Soler F; Villanueva A; Vidal A; Condom E; Ponce J; Gil J; Tortosa A; Gimenez-Bonafe P

**INSTITUCIÓN / INSTITUTION:** - Departament de Ciències Fisiològiques II, Faculty of Medicine, Campus of Health Sciences of Bellvitge, Universitat de Barcelona, IDIBELL, España.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** The objective of this study is to chemosensitize ovarian cancer (OVCa) cells to cisplatin (CDDP) using an inhibitor of Survivin, YM155. The efficacy of YM155 in combination with CDDP was determined in vitro, ex vivo and in vivo. **METHODS:** Human OVCa cell lines A2780p and their cisplatin-resistant derivative A2780cis, were treated with CDDP, YM155, and the combined treatment (YM155+CDDP), and cell viability, mRNA and protein expression levels, cell-cycle distribution, and DNA damage were then evaluated. Furthermore, the efficacy of YM155 combined with CDDP was further examined in established primary cell cultures and xenograft models. **RESULTS:** The combination of YM155 with CDDP induced G2/M cell cycle arrest and apoptosis, increased DNA damage, and decreased Survivin levels, especially in A2780cis CDDP-resistant cells. Additionally, YM155 in combination with CDDP sensitized primary cell cultures to CDDP. Studies in vivo showed how this combination significantly decreased the tumor size of OVCa xenografts. **CONCLUSIONS:** Our results demonstrate that in OVCa cells the expression of Survivin did not affect their sensitivity to YM155, suggesting that Survivin was not the only target of YM155. The combination of YM155 with CDDP could be a good option for therapy of CDDP-resistant OVCa, independently of p53 status.

[409]

**TÍTULO / TITLE:** - Synergistic cooperation between sunitinib and cisplatin promotes apoptotic cell death in human medullary thyroid cancer.

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

**REVISTA / JOURNAL:** - J Clin Endocrinol Metab. 2013 Nov 25.

●● [Enlace al texto completo \(gratis o de pago\) 1210/jc.2013-2574](#)

**AUTORES / AUTHORS:** - Lopergolo A; Nicolini V; Favini E; Dal Bo L; Tortoreto M; Cominetti D; Folini M; Perego P; Castiglioni V; Scanziani E; Grazia Borrello M; Zaffaroni N; Cassinelli G; Lanzi C

**INSTITUCIÓN / INSTITUTION:** - Molecular Pharmacology Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (AL, VN, EF, LD, MT, DC, MF, PP, NZ, GC, CL); Department of Veterinary Sciences and Public Health, Università degli Studi di Milano, Milan, Italy and Mouse & Animal Pathology Lab, Fondazione Filarete, Milan, Italy (VC, ES); Molecular Mechanisms Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (MGB).

**RESUMEN / SUMMARY:** - **Context:** Tyrosine kinase inhibitors (TKI) represent a new treatment option for patients with advanced medullary thyroid cancer (MTC). However, cures have not been achieved with current available agents used in monotherapy. **Objective:** Since RET has been shown to negatively regulate CD95 death receptor activation in preclinical models of RET-dependent MTC, we investigated the potential of the combination approach with the RET targeting TKI sunitinib and cisplatin to enhance apoptosis activation through the extrinsic pathway. **Design:** The effects of sunitinib and cisplatin were examined in human MTC cell lines harboring oncogenic

RET mutations. Experiments were designed to determine drug effects on RET signaling, cell growth, apoptosis, autophagy, tumor growth in mice, and to investigate the mechanisms of the drug interaction. Results: Sunitinib and cisplatin synergistically inhibited the growth of MZ-CRC-1 cells harboring the RET M918T activating mutation. The combination enhanced apoptosis activation through CD95-mediated, caspase-8 dependent, pathway. Moreover, sunitinib induced a severe perturbation of the autophagic flux characterized by autophagosome accumulation and a remarkable lysosomal dysfunction which was further enhanced, with lysosomal leakage induction, by cisplatin. Administration of the drug combination to mice xenografted with MZ-CRC-1 cells improved the antitumor efficacy, as compared to single agent treatments, inducing complete responses in 30% of treated mice, a significant increase in caspase-3 activation ( $P < 0.01$  vs cisplatin,  $P < 0.0005$  vs sunitinib) and apoptosis in tumor cells. Conclusions: Addition of cisplatin to sunitinib potentiates apoptotic cell death and has promising preclinical activity in MTCs harboring the RET M918T oncogene.

[410]

**TÍTULO / TITLE:** - Increased expression of stomatin-like protein 2 (STOML2) predicts decreased survival in gastric adenocarcinoma: a retrospective study.

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

**REVISTA / JOURNAL:** - Med Oncol. 2014 Jan;31(1):763. doi: 10.1007/s12032-013-0763-9. Epub 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0763-9](#)

**AUTORES / AUTHORS:** - Li XH; He F; Yan SM; Li Y; Cao Y; Huang CY; Zhou ZW

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The First Affiliated Hospital of Xiamen University, 55 Zhenhai Road, Xiamen, 361000, Fujian, People's Republic of China.

**RESUMEN / SUMMARY:** - Stomatin-like protein 2 (STOML2), a member of the stomatin, has been reported to be upregulated in several human cancers. However, its role and clinical significance in gastric adenocarcinoma remains unclear to date. The purpose of this retrospective study was to explore whether there was a correlation between the expression of STOML2 by immunohistochemistry and the clinical outcome of a large group of patients with gastric adenocarcinoma. In this retrospective study, we performed immunohistochemistry to evaluation of STOML2 expression in a large panel of gastric adenocarcinoma samples. The receiver operating characteristic method was used to define the STOML2 immunoreactivity score cutoff value. The clinical/prognostic significance of STOML2 expression was analyzed statistically. Kaplan-Meier analysis was used to compare the postoperative survival between groups. STOML2 was overexpressed in gastric cancer compared with paracancerous normal mucosa. Increased STOML2 expression was associated with higher histologic grade ( $P = 0.047$ ), T category ( $P < 0.001$ ), and N category ( $P = 0.01$ ). Patients with high expression of STOML2 demonstrated shortened overall survival compared with those with low expression of STOML2 (median of 38.9 vs. 64.0 months,  $P < 0.001$ ). Furthermore, STOML2 expression could stratify patients survival in stage N0 ( $P < 0.001$ ). Multivariate analysis showed that the level of STOML2 expression was an independent prognostic factor in gastric adenocarcinoma (RR = 1.920,  $P = 0.001$ ). Increased expression of STOML2 suggests unfavorable prognosis for gastric adenocarcinoma patients. Further studies are warranted.

[411]

**TÍTULO / TITLE:** - Histone acetylation and arachidonic acid cytotoxicity in HepG2 cells overexpressing CYP2E1.

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

**REVISTA / JOURNAL:** - Naunyn Schmiedebergs Arch Pharmacol. 2013 Nov 28.

●● Enlace al texto completo (gratis o de pago) [1007/s00210-013-0942-4](#)

**AUTORES / AUTHORS:** - Holownia A; Mroz RM; Wielgat P; Jakubow P; Jablonski J; Sulek J; Braszko JJ

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Pharmacology, Medical University of Bialystok, Waszyngtona 15A, 15-274, Bialystok, Poland, [Holow\\_sinai@hotmail.com](mailto:Holow_sinai@hotmail.com).

**RESUMEN / SUMMARY:** - The aim of this work was to assess the role of ethanol-derived acetate and acetate-mediated histone acetylation in arachidonic acid-induced stress in HepG2 cells and cells overexpressing CYP2E1. Cells were grown for 7 days with 1 mM sodium acetate or 100 mM ethanol; their acetylated histone proteins and histone deacetylase 2 expression was quantified using Western blot. Ethanol- or acetate-pretreated cells were also treated for 24 h with 60 μM arachidonic acid to induce oxidative stress. Cytotoxicity was estimated by lactate dehydrogenase release, 3-[4,5-dimethylthiazolyl-2] 2,5-diphenyltetrazolium bromide test, and by DNA damage, while oxidative stress was quantified using dichlorofluorescein diacetate. Cells grown with ethanol or acetate had increased acetylated histone H3 levels in both cell types and elevated acetylated histone H4 levels in cells overexpressing CYP2E1 but not in naive cells. In cells overexpressing CYP2E1 grown with ethanol, expression of histone deacetylase 2 was reduced by about 40 %. Arachidonic acid altered cell proliferation and was cytotoxic mostly to cells engineered to overexpress CYP2E1 but both effects were significantly lower in cells pretreated with ethanol or acetate. Cytotoxicity was also significantly decreased by 4-methylpyrazole-a CYP2E1 inhibitor and by trichostatin-an inhibitor of histone deacetylases. In cells pretreated with acetate or ethanol, the oxidative stress induced by arachidonic acid was also significantly lower. Our data indicate that histone hyperacetylation may in some extent protect the cells against oxidative stress. It is possible that acetate may act as an antioxidant at histone level. This mechanism may be relevant to alcohol-induced liver injury.

[412]

**TÍTULO / TITLE:** - Heart remodeling induced by adjuvant trastuzumab-containing chemotherapy for breast cancer overexpressing human epidermal growth factor receptor type 2: A prospective study.

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

**REVISTA / JOURNAL:** - Pharmacol Res. 2013 Dec;78:41-8. doi: 10.1016/j.phrs.2013.10.001. Epub 2013 Oct 27.

●● Enlace al texto completo (gratis o de pago) [1016/j.phrs.2013.10.001](#)

**AUTORES / AUTHORS:** - Piotrowski G; Gawor R; Bourge RC; Stasiak A; Potemski P; Gawor Z; Nanda NC; Banach M

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiology, N. Copernicus Memorial Hospital, Lodz, Poland. Electronic address: [gpiotr4@wp.pl](mailto:gpiotr4@wp.pl).

**RESUMEN / SUMMARY:** - We aimed to investigate the cardiac changes in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer treated with trastuzumab in an adjuvant setting. Two hundred and fifty-three women with HER2-positive breast cancer were included. The assessment of cardiovascular system and echocardiography were performed and compared at baseline, at the termination of trastuzumab therapy and 6 months later. Left heart remodeling was defined arbitrary as the change in at least one of the analyzed echocardiographic parameters of  $\geq$ standard deviation (SD) (in model I) or  $\geq 2 \times$ SD (in model II) after 6-month follow-up. After 6-month follow-up 39 (31.7%), 27 (22%), 14 (11.4%), 10 (8.1%), 5 (4.1%) and 1 (0.8%), women had at least one parameter with a change exceeding mean difference  $\geq$ SD, respectively; and 30 (24.4%), 9 (7.5%), 3 (2.4%), 2 (1.6%) 1 (0.8%) exceeding mean difference  $\geq 2$ SD. In stepwise multivariate regression analysis sedentary life style (OR 16.7,  $p=0.003$ ), positive cardiovascular family history (OR 6.9;  $p=0.013$ ) and left ventricular ejection fraction change after 3 months (OR 1.2;  $p=0.007$ ) were independent predictors of left heart remodeling in model I, whereas hypertension (OR 5.6;  $p=0.06$ ) and positive cardiovascular family history (OR 3.9;  $p=0.032$ ) were independent predictors of heart remodeling in model II. In conclusion, trastuzumab induces LV and left atrial cavity dilatation together with LV systolic function impairment.

[413]

**TÍTULO / TITLE:** - Piperine induces apoptosis of lung cancer A549 cells via p53-dependent mitochondrial signaling pathway.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 24.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1433-4](#)

**AUTORES / AUTHORS:** - Lin Y; Xu J; Liao H; Li L; Pan L

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiothoracic Surgery, 306 Hospital of PLA, Beijing, 100101, China.

**RESUMEN / SUMMARY:** - The aim of this study was to evaluate the cytotoxic and apoptotic effects of piperine on human lung cancer A549 cells and to explore its mechanisms. Piperine was found to exert the greatest cytotoxic effect against A549 cells in a dose-dependent manner, whereas it showed no effect on WI38 human lung fibroblasts. This cell growth-inhibitory effect might be attributed to cell DNA damage and cytotoxic effects. Besides, piperine had the ability to cause cell cycle arrest in G2/M phase and to activate caspase-3 and caspase-9 cascades in A549 cells. Furthermore, piperine-induced apoptosis could be blocked by the broad caspase inhibitor z-VAD-fmk in majority. In addition, piperine treatment decreased Bcl-2 protein expression, but increased Bax protein expression in A549 cells, which were positively correlated with an elevated expression of p53 compared to control. Taken together, these results suggested that piperine could induce p53-mediated cell cycle arrest and apoptosis via activation of caspase-3 and caspase-9 cascades, as well as increasing the Bax/Bcl-2 ratio. Thus, piperine could be developed as an effective antitumor agent in the prevention and treatment of lung cancer without toxicity to the host.

[414]

**TÍTULO / TITLE:** - Investigation of quinazolines as inhibitors of breast cancer resistance protein (ABCG2).

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

**REVISTA / JOURNAL:** - Bioorg Med Chem. 2013 Dec 15;21(24):7858-73. doi: 10.1016/j.bmc.2013.10.007. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmc.2013.10.007](#)

**AUTORES / AUTHORS:** - Juvale K; Gallus J; Wiese M

**INSTITUCIÓN / INSTITUTION:** - Pharmaceutical Institute, University of Bonn, Pharmaceutical Chemistry II, An der Immenburg 4, 53121 Bonn, Germany.

**RESUMEN / SUMMARY:** - Chemotherapy is one of the major forms of cancer treatment. Unfortunately, tumors are prone to multidrug resistance leading to failure of treatment. Breast cancer resistance protein (BCRP), the second member of ABC transporter subfamily G, has been found to play a major role in drug efflux and hence multidrug resistance. Until now, very few potent and selective BCRP inhibitors like Ko143 have been identified. In the search for more potent and selective BCRP inhibitors, we synthesized and investigated a series of differently substituted quinazoline compounds. Several variations at positions 2, 4, 6 and 7 of the quinazoline scaffold were carried out to develop a structure-activity-relationship analysis for these compounds. It was found that compounds bearing a phenyl substituent at position 2 of the 4-anilinoquinazoline scaffold were most potent. On the aniline ring at position 4 of the quinazoline moiety substituents like NO<sub>2</sub>, CN, CF<sub>3</sub> led to very high BCRP inhibition potencies. The most potent compounds were further investigated for their intrinsic cytotoxicity and their ability to reverse the multidrug resistance. Compound 20, an anilinoquinazoline bearing a phenyl ring at position 2 and meta-nitro substitution on the 4-anilino ring, was found to have the highest therapeutic ratio. The most active compounds from each variation were also investigated for their effect on BCRP expression. It was found that compound 20 has no significant effect on BCRP expression, while compound 31 decreased the surface BCRP expression. The only difference in the two compounds was the presence of a 3,4-dimethoxyphenyl ring in compound 31 instead of phenyl substitution at position 2 of the quinazoline moiety. From the study of all target compounds, compound 20 was the most prominent compound having inhibitory potency even higher than Ko143, the most potent BCRP inhibitor known. Compound 20 was also found to be selective towards BCRP with a very high therapeutic ratio.

[415]

**TÍTULO / TITLE:** - Histone deacetylase inhibitors induce apoptosis in myeloid leukemia by suppressing autophagy.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Sep 12. doi: 10.1038/leu.2013.264.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.264](#)

**AUTORES / AUTHORS:** - Stankov MV; El Khatib M; Kumar Thakur B; Heitmann K; Panayotova-Dimitrova D; Schoening J; Bourquin JP; Schweitzer N; Leverkus M; Welte K; Reinhardt D; Li Z; Orkin SH; Behrens GM; Klusmann JH

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Immunology and Rheumatology, Hannover Medical School, Hannover, Germany.

**RESUMEN / SUMMARY:** - Histone deacetylase (HDAC) inhibitors (HDACis) are well-characterized anti-cancer agents with promising results in clinical trials. However,

mechanistically little is known regarding their selectivity in killing malignant cells while sparing normal cells. Gene expression-based chemical genomics identified HDACis as being particularly potent against Down syndrome-associated myeloid leukemia (DS-AMKL) blasts. Investigating the antileukemic function of HDACis revealed their transcriptional and post-translational regulation of key autophagic proteins, including ATG7. This leads to suppression of autophagy, a lysosomal degradation process that can protect cells against damaged or unnecessary organelles and protein aggregates. DS-AMKL cells exhibit low baseline autophagy due to mammalian target of rapamycin (mTOR) activation. Consequently, HDAC inhibition repressed autophagy below a critical threshold, which resulted in accumulation of mitochondria, production of reactive oxygen species, DNA damage and apoptosis. Those HDACi-mediated effects could be reverted upon autophagy activation or aggravated upon further pharmacological or genetic inhibition. Our findings were further extended to other major acute myeloid leukemia subgroups with low basal level autophagy. The constitutive suppression of autophagy due to mTOR activation represents an inherent difference between cancer and normal cells. Thus, via autophagy suppression, HDACis deprive cells of an essential pro-survival mechanism, which translates into an attractive strategy to specifically target cancer cells. Leukemia advance online publication, 1 October 2013; doi:10.1038/leu.2013.264.

[416]

**TÍTULO / TITLE:** - Thymidylate synthase, topoisomerase-1 and microsatellite instability: relationship with outcome in mucinous colorectal cancer treated with fluorouracil.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4611-7.

**AUTORES / AUTHORS:** - Negri FV; Azzoni C; Bottarelli L; Campanini N; Mandolesi A; Wotherspoon A; Cunningham D; Scartozzi M; Cascinu S; Tinelli C; Silini EM; Ardizzoni A

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Unit, University Hospital, Via Gramsci 14, 43126 Parma, Italy. [francescanegri2@hotmail.com](mailto:francescanegri2@hotmail.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Mucinous colorectal cancer (CRC) exhibits distinct clinical and pathological features, including poorer response to fluorouracil (FU) compared with non-mucinous tumours. PATIENTS AND METHODS: We compared the expression of thymidylate synthase (TYMS) and topoisomerase-1 (TOPO1) and DNA microsatellite instability (MSI) in 87 patients (35 mucinous and 52 non-mucinous CRCs) enrolled in three randomized trials, evaluating infused FU as first-line treatment. RESULTS: Mucinous CRCs more frequently had high TOPO1 expression than did non-mucinous tumors (41% vs. 15%,  $p=0.028$ ). The median overall survival was 14.2 months for patients with mucinous CRC with low TOPO1 expression compared with 9.7 months for high TOPO1-expressing cases ( $p=0.016$ ). After adjusting for confounding variables, low TOPO1 expression was statistically favourably associated with overall survival (hazard ratio=0.55;  $p=0.041$ ). CONCLUSION: Our data suggest the TOPO1 expression levels to be a prognostic marker in patients with mucinous CRC treated with FU. If further verified, these data might redefine therapeutic strategies by identifying categories of patients with a worse prognosis.

[417]

**TÍTULO / TITLE:** - Fibronectin overexpression is associated with latent membrane protein 1 expression and has independent prognostic value for nasopharyngeal carcinoma.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1235-8](#)

**AUTORES / AUTHORS:** - Ma LJ; Lee SW; Lin LC; Chen TJ; Chang IW; Hsu HP; Chang KY; Huang HY; Li CF

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Chi-Mei Foundation Medical Center, Tainan, Taiwan.

**RESUMEN / SUMMARY:** - Despite recent improvements in the diagnosis and treatment, the final outcomes in patients with nasopharyngeal carcinomas (NPC) still remain suboptimal. Through data mining from published transcriptomic database with further bioinformatic validation, fibronectin (FN1) was identified as a differentially upregulated gene in NPC tissues, which implicates the transition from epithelial to mesenchymal phenotype (EMT) and promotes metastasis. Given the roles of fibronectin in risk stratification and in the frontline therapeutics of common carcinomas, such as renal cell cancer, we explored fibronectin immunorexpression status and its associations with clinicopathological variables and survival in a well-defined cohort of NPC patients. Fibronectin immunohistochemistry was retrospectively performed and analyzed using H-score for 124 biopsy specimens from NPC patients who received standard treatment without distant metastasis at initial diagnosis. Those cases with H-score higher than the median value were regarded as fibronectin overexpression. The findings were correlated with clinicopathological variables, EBV latent membrane protein 1 (LMP1) expression, disease-specific survival (DSS), distant metastasis-free survival (DMFS), and local recurrence-free survival (LRFS). Fibronectin overexpression was significantly associated with American Joint Committee on Cancer (AJCC) stages III-IV ( $p = 0.019$ ) and LMP1 expression ( $p = 0.004$ ), and univariately predictive of adverse outcomes for DSS, DMFS, and LRFS (all  $p < 0.0001$ ). In the multivariate comparison, fibronectin overexpression still remained prognostically independent to portend worse DSS ( $p < 0.01$ , hazard ratio = 5.958), DMFS ( $p < 0.01$ , hazard ratio = 5.728), and LRFS ( $p < 0.01$ , hazard ratio = 5.411) together with advanced AJCC stages III-IV. Fibronectin is upregulated in a subset of NPCs, and its increased immunorexpression significantly correlated with advanced features, justifying the potentiality of fibronectin as a theragnostic biomaker of NPC.

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[418]

**TÍTULO / TITLE:** - Rottlerin induces autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Oct 11. pii: S0304-3835(13)00714-3. doi: 10.1016/j.canlet.2013.10.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.10.003](#)

**AUTORES / AUTHORS:** - Kumar D; Shankar S; Srivastava RK

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, Toxicology and Therapeutics, and Medicine, The University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, 66160, USA. Electronic address: [dkumar2@kumc.edu](mailto:dkumar2@kumc.edu).

**RESUMEN / SUMMARY:** - Autophagy plays an important role in cellular homeostasis through the disposal and recycling of cellular components. Cancer stem cells (CSCs) play major roles in cancer initiation, progression, and drug resistance. Rottlerin (Rott) is an active molecule isolated from *Mallotus philippinensis*, a medicinal plant used in Ayurvedic Medicine for anti-allergic and anti-helminthic treatments, demonstrates anticancer activities. However, the molecular mechanisms by which it induces autophagy in prostate CSCs have not been examined. The main objective of the paper was to examine the molecular mechanisms by which Rott induces autophagy in prostate CSCs. Autophagy was measured by the lipid modification of light chain-3 (LC3) and the formation of autophagosomes. Apoptosis was measured by flow cytometer analysis. The Western blot analysis was used to examine the effects of Rott on the expression of PI3K, phosphorylation of Akt, phosphorylation of mTOR, and phosphorylation of AMPK in pros CSCs. RNAi technology was used to inhibit the expression of Beclin-1 and ATG-7. Rott induced the lipid modification of light chain-3 (LC3) and the formation of autophagosomes after 24h of Rott treatment in prostate CSCs. Rott-treated prostate CSCs induced transition from LC3-I to LC3-II, a hall mark of autophagy. Rott also induced the expression of Atg5, Atg7, Atg12 and Beclin-1 proteins during autophagy. The knock-down of Atg7 and Beclin-1 blocked Rott-induced autophagy. Furthermore, Rott induced AMPK phosphorylation was blocked by 3-MA, Baf and CHX. In addition, inhibition of AMPK expression by shRNA blocked Rott induced autophagy. In conclusion, a better understanding of the biology of autophagy and the pharmacology of autophagy modulators has the potential for facilitating the development of autophagy-based therapeutic interventions for prostate cancer.

[419]

**TÍTULO / TITLE:** - KRAS-mutated plasma DNA as predictor of outcome from irinotecan monotherapy in metastatic colorectal cancer.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 21. doi: 10.1038/bjc.2013.633.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.633](#)

**AUTORES / AUTHORS:** - Spindler KG; Appelt AL; Pallisgaard N; Andersen RF; Jakobsen A

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Oncology, Vejle Hospital, Vejle, Denmark [2] Danish Colorectal Cancer Group South, Vejle Hospital, Kabbeltøft 25, 7100, Vejle, Denmark.

**RESUMEN / SUMMARY:** - Background: We investigated the clinical implications of KRAS and BRAF mutations detected in both archival tumor tissue and plasma cell-free DNA in metastatic colorectal cancer patients treated with irinotecan monotherapy. Methods: Two hundred and eleven patients receiving second-line irinotecan (350 mg m<sup>-2</sup> q3w) were included in two independent cohorts. Plasma was obtained from pretreatment EDTA blood-samples. Mutations were detected in archival tumour and plasma with qPCR methods. Results: Mutation status in tumor did not correlate to efficacy in either cohort, whereas none of the patients with mutations detectable in plasma responded to therapy. Response rate and disease control rate in

plasma KRAS wt patients were 19 and 66% compared with 0 and 37%, in patients with pKRAS mutations, (P=0.04 and 0.01). Tumor KRAS status was not associated with PFS but with OS in the validation cohort. Plasma BRAF and KRAS demonstrated a strong influence on both PFS and OS. The median OS was 13.0 mo in pKRAS wt patients and 7.8 in pKRAS-mutated, (HR=2.26, P<0.0001). PFS was 4.6 and 2.7 mo, respectively (HR=1.69, P=0.01). Multivariate analysis confirmed the independent prognostic value of pKRAS status but not KRAS tumor status. Conclusion: Tumor KRAS has minor clinical impact, whereas plasma KRAS status seems to hold important predictive and prognostic information. British Journal of Cancer advance online publication, 21 November 2013; doi:10.1038/bjc.2013.633 [www.bjcancer.com](http://www.bjcancer.com).

[420]

**TÍTULO / TITLE:** - Additive effect of the AZGP1, PIP, S100A8, and UBE2C molecular biomarkers improves outcome prediction in breast carcinoma.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Oct 1. doi: 10.1002/ijc.28497.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ijc.28497](#)

**AUTORES / AUTHORS:** - Parris TZ; Kovacs A; Aziz L; Hajizadeh S; Nemes S; Semaan M; Forssell-Aronsson E; Karlsson P; Helou K

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Cancer Center, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

**RESUMEN / SUMMARY:** - The deregulation of key cellular pathways is fundamental for the survival and expansion of neoplastic cells, which in turn can have a detrimental effect on patient outcome. To develop effective individualized cancer therapies, we need to have a better understanding of which cellular pathways are perturbed in a genetically defined subgroup of patients. Here, we validate the prognostic value of a 13-marker signature in independent gene expression microarray datasets (n = 1,141) and immunohistochemistry with full-faced FFPE samples (n = 71). The predictive performance of individual markers and panels containing multiple markers was assessed using Cox regression analysis. In the external gene expression dataset, six of the 13 genes (AZGP1, NME5, S100A8, SCUBE2, STC2, and UBE2C) retained their prognostic potential and were significantly associated with disease-free survival (P < 0.001). Protein analyses refined the signature to a four-marker panel (AZGP1, PIP, S100A8, and UBE2C) significantly correlated with cycling, high grade tumors and lower disease-specific survival rates. AZGP1 and PIP were found in significantly lower levels in invasive breast tissue compared with adjacent normal tissue, whereas elevated levels of S100A8 and UBE2C were observed. A predictive model containing the four-marker panel in conjunction with established clinical variables outperformed a model containing the clinical variables alone. Our findings suggest that deregulated AZGP1, PIP, S100A8, and UBE2C are critical for the aggressive breast cancer phenotype, which may be useful as novel therapeutic targets for drug development to complement established clinical variables. © 2013 Wiley Periodicals, Inc.

[421]

**TÍTULO / TITLE:** - Sinodielide A exerts thermosensitizing effects and induces apoptosis and G2/M cell cycle arrest in DU145 human prostate cancer cells via the Ras/Raf/MAPK and PI3K/Akt signaling pathways.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Nov 27. doi: 10.3892/ijmm.2013.1568.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1568](#)

**AUTORES / AUTHORS:** - Hatashita M; Taniguchi M; Baba K; Koshiha K; Sato T; Jujo Y; Suzuki R; Hayashi S

**INSTITUCIÓN / INSTITUTION:** - Research and Development Department, The Wakasa Wan Energy Research Center, Tsuruga, Fukui 914-0192, Japan.

**RESUMEN / SUMMARY:** - Sinodielide A (SA) is a naturally occurring guaianolide, which is isolated from the root of *Sinodielsia yunnanensis*. This root, commonly found in Yunnan province, is used in traditional Chinese medicine as an antipyretic, analgesic and diaphoretic agent. A number of studies have reported that agents isolated from a species of Umbelliferae (Apiaceae) have antitumor activities. We previously reported, using combined treatments with this medicinal herb and hyperthermia at various temperatures, an enhanced cytotoxicity in the human prostate cancer androgen-independent cell lines, PC3 and DU145, and analyzed the related mechanisms. In the present study, we investigated the effects of treatment with SA prior to hyperthermia on the thermosensitivity of DU145 cells, and the mechanisms related to the induction of apoptosis and G2/M cell cycle arrest via the activation of extracellular-regulated kinase (ERK)1/2, c-Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) signaling pathways, as well as the phosphoinositide 3-kinase (PI3K)/Akt signaling pathways. Cells were exposed to hyperthermia alone (40-44 C) or hyperthermia in combination with SA. Lethal damage to cells treated with mild hyperthermia (40 or 42 C) for up to 6 h was slight; however, hyperthermia in combination with SA synergistically enhanced thermosensitivity. Lethal damage to cells treated with acute hyperthermia (43 or 44 C) was more severe, but these effects were also enhanced and were more significant by the combined treatment with SA. The kinetics of apoptosis induction and cell cycle distribution were analyzed by flow cytometry. In addition, the levels of ERK1/2, JNK and Akt were determined by western blot analysis. The incidence of apoptotic cells after treatment with SA (20.0 microM) at 37 C for 4 h, hyperthermia (44 C) alone for 30 min, and the combination in sequence were examined. The sub-G1 division (%) in the diagram obtained by flow cytometry was applied to that assay. The percentage of apoptotic cells (10.53+/-5.02%) was higher at 48 h as compared to 0, 12 and 24 h after treatment. The distribution of DU145 cells in the G2/M cell cycle phase was markedly increased after 24 h of heating at 44 C and after the combined treatment with heating and SA. The phosphorylation of ERK1/2 was reduced following treatment with heating and SA, while the levels of phosphorylated JNK (p-JNK) were markedly increased immediately after heating at 44 C and when heating was combined with SA. By contrast, the levels of phosphorylated Akt (p-Akt) were immediately increased only after heating at 44 C. Thus, we concluded that SA exerts its thermosensitizing effects on DU145 cells by inhibiting the activation of the MAPK/ERK1/2 and PI3K/Akt signaling pathways.

**TÍTULO / TITLE:** - Profiling the molecular mechanism of fullerene cytotoxicity on tumor cells by RNA-seq.

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

**REVISTA / JOURNAL:** - Toxicology. 2013 Dec 6;314(1):183-92. doi: 10.1016/j.tox.2013.10.001. Epub 2013 Oct 12.

●● Enlace al texto completo (gratis o de pago) [1016/j.tox.2013.10.001](#)

**AUTORES / AUTHORS:** - Lucafo M; Gerdol M; Pallavicini A; Pacor S; Zorzet S; Da Ros T; Prato M; Sava G

**INSTITUCIÓN / INSTITUTION:** - Department of Life Sciences, University of Trieste, Via Giorgieri 5, 34127 Trieste (TS), Italy. Electronic address: [marianna.lucafo@phd.units.it](mailto:marianna.lucafo@phd.units.it).

**RESUMEN / SUMMARY:** - The interest on functionalized fullerenes in the field of nanomedicine has seen a significant increase in the past decade. However, the different methods employed to increase C60 solubility profoundly influence the physicochemical properties and the toxicological effects of these compounds, thus complicating the evaluation of their toxicity and potential therapeutic use. Here we report a whole-transcriptome RNA-seq analysis assessing the effect of two fullerenes (1 and 2) on gene expression in the human MCF7 cell line. Although these two compounds had previously been characterized by in vitro studies as having a cytotoxic and null effect respectively, to date the mechanisms at the basis of this different behavior and, more in general, at the basis of the effect of most fullerene derivatives in living cells are still completely unknown. Our data evidence that: (a) fullerene 2 caused a significant, time-dependent alteration of gene expression, whereas 1 only had a negligible effect; (b) the biological processes mostly influenced over the 48h experimental time course were transcription, protein synthesis, cell cycle progression and cell adhesion; (c) the gene expression signature of 2-treated cells was strikingly similar to those induced by selective inhibitors of mTOR signaling, thus suggesting an effect on this pathway for fullerene 2. Our work represents the first approach toward the application of RNA-seq to the study of the molecular mechanisms underlying the interaction of fullerenes with cellular systems and provides an objective view of the feasibility and the safety of these nanomaterials for a medical application.

[423]

**TÍTULO / TITLE:** - A study to investigate dose escalation of doxorubicin in ABVD chemotherapy for Hodgkin lymphoma incorporating biomarkers of response and toxicity.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 12;109(10):2560-5. doi: 10.1038/bjc.2013.605. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.605](#)

**AUTORES / AUTHORS:** - Gibb A; Greystoke A; Ranson M; Linton K; Neeson S; Hampson G; Illidge T; Smith E; Dive C; Pettitt A; Lister A; Johnson P; Radford J

**INSTITUCIÓN / INSTITUTION:** - Departments of Medical and Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK.

**RESUMEN / SUMMARY:** - Background: Myelotoxicity during initial cycles of chemotherapy for Hodgkin lymphoma is associated with better outcome, supporting the concept of individualised dosing based on pharmacodynamic end points to optimise results. This study was performed to identify the maximum tolerated dose (MTD) of

doxorubicin within cycles 1-3 ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Circulating biomarkers of response (nucleosomal DNA, nDNA) and epithelial toxicity (Cytokeratin 18, CK18) were also measured. Methods: Dose escalation of doxorubicin in cycles 1-3 ABVD supported by pegfilgrastim was performed on a six-patient cohort basis (35, 45 and 55 mg m<sup>-2</sup>) with doxorubicin reduced to 25 mg m<sup>-2</sup> or omitted in cycles 4-6 to maintain cumulative exposure of 103-130% standard ABVD. BVD was given at standard doses throughout. Six additional subjects were recruited at the MTD. Results: Twenty-four subjects were recruited. Dose-limiting toxicities (DLTs) of grade 3 neuropathy, pneumonitis, palmar-plantar erythema and neutropenic infection were observed at 55 mg m<sup>-2</sup>, so 45 mg m<sup>-2</sup> was declared the MTD. In patients who subsequently experienced DLT at any time, large increases in CK18 were seen on day 3 of cycle 1 ABVD. Conclusion: Escalated ABVD incorporating doxorubicin at 45 mg m<sup>-2</sup> in cycles 1-3 can be delivered safely with pegfilgrastim support. Circulating cell death biomarkers may assist in the development of future individualised dosing strategies.

[424]

**TÍTULO / TITLE:** - An anti-leishmanial thiadiazine agent induces multiple myeloma cell apoptosis by suppressing the nuclear factor kappaB signalling pathway.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 14. doi: 10.1038/bjc.2013.711.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.711](#)

**AUTORES / AUTHORS:** - Chen G; Han K; Xu X; Du X; Zhang Z; Tang J; Shi M; Wang M; Li J; Cao B; Mao X

**INSTITUCIÓN / INSTITUTION:** - Cyrus Tang Hematology Center, Soochow University, Suzhou 215123, China.

**RESUMEN / SUMMARY:** - Background: Nuclear factor kappaB (NFkappaB) has a critical role in the pathophysiology of multiple myeloma. Targeting NFkappaB is an important strategy for anti-myeloma drug discovery. Methods: Luciferase assay was used to evaluate the effects of DETT on NFkappaB activity. Annexin V-PI double staining and immunoblotting were used to evaluate DETT-induced cell apoptosis and suppression of NFkappaB signalling. Anti-myeloma activity was studied in nude mice. Results: DETT downregulated IKKalpha, beta, p65, and p50 expression and inhibited phosphorylation of p65 (Ser536) and IkappaBalpha. Simultaneously, DETT increased IkappaBalpha, an inhibitor of the p65/p50 heterodimer, even in the presence of stimulants lipopolysaccharide, tumour necrosis factor-alpha, or interleukin-6. DETT inhibited NFkappaB transcription activity and downregulated NFkappaB-targeted genes, including Bcl-2, Bcl-XL, and XIAP as measured by their protein expression. Deregulation of NFkappaB signalling by DETT resulted in MM cell apoptosis characterised by cleavage of caspase-3, caspase-8, and PARP. Notably, this apoptosis was partly blocked by the activation of NFkappaB signalling in the presence of TNFalpha and IL-6. Moreover, DETT delayed myeloma tumour growth in nude mice without overt toxicity. Conclusion: DETT displays a promising potential for MM therapy as an inhibitor of the NFkappaB signalling pathway. British Journal of Cancer advance online publication, 14 November 2013; doi:10.1038/bjc.2013.711 [www.bjcancer.com](http://www.bjcancer.com).

[425]

**TÍTULO / TITLE:** - Prognostic Significance of Pretreatment Serum Cytokines in Classical Hodgkin Lymphoma.

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

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

- Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1879](#)

**AUTORES / AUTHORS:** - Marri PR; Hodge LS; Maurer MJ; Ziesmer SC; Slager SL; Habermann TM; Link BK; Cerhan JR; Novak AJ; Ansell SM

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Divisions of Hematology and Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; and Department of Internal Medicine, College of Medicine, University of Iowa, Iowa City, Iowa.

**RESUMEN / SUMMARY:** - PURPOSE: Although the International Prognostic Score (IPS) is the gold standard for risk-stratifying patients with classical Hodgkin lymphoma (cHL), these criteria do not accurately predict outcome. As cytokines are critically involved in driving cHL, we tested whether pretreatment serum cytokine levels could provide additional prognostic information. EXPERIMENTAL DESIGN: Thirty cytokines were measured in pretreatment serum from 140 patients with cHL and compared with 50 nonlymphoma controls. Patients were followed for event-free survival (EFS) and overall survival (OS), and Cox proportional hazards regression models were used to assess the association of individual cytokines and the cytokine profiles with outcome via unadjusted and IPS-adjusted HR. RESULTS: Twelve cytokines (EGF, bFGF, G-CSF, HGF, IL-6, IL-8, IL-12, IL-2R, IP-10, MIG, TNF-alpha, and VEGF) were significantly ( $P < 0.05$ ) higher in patients with cHL than controls; elevated levels of HGF, IL-6, IL-2R, IP-10, and MIG were all associated with poorer EFS. Only interleukin-2 receptor (IL-2R;  $P = 0.002$ ) and interleukin (IL)-6 ( $P < 0.001$ ) were independently prognostic. Patients with increased IL-6 and IL-2R had a significantly higher risk of early relapse and death, a finding that remained significant even after IPS-based risk stratification. Although elevated IL-6 and IL-2R correlated with the IPS, soluble CD30 (sCD30), and thymus and activation-related chemokine (TARC) levels, the two-cytokine model remained independently predictive of prognosis. CONCLUSIONS: Elevated pretreatment serum cytokines are associated with increased disease relapse and inferior survival in cHL. Thus, the pretreatment cytokine profile, particularly serum levels of IL-6 and IL-2R, may be used to identify patients with cHL at high risk for early-disease relapse. Clin Cancer Res; 1-8. ©2013 AACR.

[426]

**TÍTULO / TITLE:** - Molecular biomarkers of prognosis in melanoma: how far are we from the clinic?

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

**REVISTA / JOURNAL:** - Melanoma Res. 2013 Dec;23(6):423-5. doi: 10.1097/CMR.0000000000000001.

- Enlace al texto completo (gratis o de pago)

[1097/CMR.0000000000000001](#)

**AUTORES / AUTHORS:** - Schramm SJ; Menzies AM; Mann GJ

**INSTITUCIÓN / INSTITUTION:** - aThe University of Sydney at Westmead Millennium Institute for Medical Research bMelanoma Institute Australia, Sydney, New South Wales, Australia.

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[427]

**TÍTULO / TITLE:** - TNFR1/TNF-alpha and mitochondria interrelated signaling pathway mediates quinocetone-induced apoptosis in HepG2 cells.

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

**REVISTA / JOURNAL:** - Food Chem Toxicol. 2013 Dec;62:825-38. doi: 10.1016/j.fct.2013.10.022. Epub 2013 Oct 22.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.10.022](#)

**AUTORES / AUTHORS:** - Zhang C; Wang C; Tang S; Sun Y; Zhao D; Zhang S; Deng S; Zhou Y; Xiao X

**INSTITUCIÓN / INSTITUTION:** - Dept. of Pharmacology and Toxicology, College of Veterinary Medicine, China Agricultural University, Yuanmingyuan West Road No. 2, Haidian District, Beijing 100193, PR China. Electronic address: [zcmcau@gmail.com](mailto:zcmcau@gmail.com).

**RESUMEN / SUMMARY:** - Quinocetone, a new quinoxaline 1, 4-dioxide derivative, has been widely used as an animal feed additive in China. This study was conducted to explore the molecular mechanisms of apoptosis induced by quinocetone in HepG2 cells. MTT assay revealed that the viability of HepG2 cells was significantly inhibited by quinocetone in a dose- and time-dependent manner. Quinocetone-induced apoptosis in HepG2 cells was characterized by cell and nuclei morphology change, cell membrane phosphatidylserine translocation, DNA fragmentation, cleavage of poly (ADP-ribose) polymerase (PARP) and a cascade activation of caspase-8, caspase-9 and caspase-3. Simultaneously, quinocetone induced HepG2 cell cycle arrest, which was supported by overexpression of p21. Cytochrome c release was caused by the mitochondrial membrane potential dissipation, a process related to quinocetone-induced Bid cleavage and elevated Bax/Bcl-2 ratio. Moreover, quinocetone treatment caused the up-regulation of TNF-alpha and TNFR1 in HepG2 cells. Both soluble TNFR1 receptors and caspase inhibitors suppressed quinocetone-induced apoptosis. In addition, the protein levels of p53, p-p38 and p-JNK were increased in quinocetone-treated cells. Taken together, quinocetone induced apoptosis in HepG2 cells via activation of caspase, interaction of TNF-alpha and TNFR1 and modulation of the protein levels of Bid, Bax and Bcl-2, involving the participation of p53, p38 and JNK.

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[428]

**TÍTULO / TITLE:** - Anti-tumor activity of the X-linked inhibitor of apoptosis (XIAP) inhibitor embelin in gastric cancer cells.

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

**REVISTA / JOURNAL:** - Mol Cell Biochem. 2013 Oct 18.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1853-x](#)

**AUTORES / AUTHORS:** - Wang DG; Sun YB; Ye F; Li W; Kharbuja P; Gao L; Zhang DY; Suo J

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, The First Hospital, Jilin University, Changchun, 130021, Jilin, China.

**RESUMEN / SUMMARY:** - This study investigated the anticancer effects of embelin in human gastric cancer cells and the underlying molecular mechanisms. Gastric cancer cells were treated with embelin and 5-FU for methyl-thiazolyl-tetrazolium bromide cell viability assay and flow cytometric detection of cell viability and apoptosis. Protein pathway array (PPA) and Western blot were used to investigate differentially expressed proteins in embelin-treated gastric cancer cells. Embelin reduced gastric cancer cell viability, induced apoptosis, and enhanced 5-FU antitumor activity in gastric cancer cells. Mechanistically, embelin induced cell cycle arrest at the S and G2/M phases. Molecularly, embelin downregulated expression of X-linked inhibitor of apoptosis and cell cycle-regulatory proteins, such as CDK1, CDC25B, CDC25C, cyclinB1, and CDK2. PPA analysis showed that embelin modulated several pathways that are associated with cell growth and apoptosis, such as PI3K/AKT, JAK/STAT, p38 MAPK, and p53. The data from the current study implied that reduction of gastric cancer cell viability after treatment with embelin was through cell cycle arrest at the S and G2/M phases and apoptosis.

[429]

**TÍTULO / TITLE:** - Inhibition of autophagy enhances apoptosis induced by proteasome inhibitor bortezomib in human glioblastoma U87 and U251 cells.

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

**REVISTA / JOURNAL:** - Mol Cell Biochem. 2014 Jan;385(1-2):265-75. doi: 10.1007/s11010-013-1835-z. Epub 2013 Oct 9.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11010-013-1835-z](#)

**AUTORES / AUTHORS:** - Zhang X; Li W; Wang C; Leng X; Lian S; Feng J; Li J; Wang H

**INSTITUCIÓN / INSTITUTION:** - Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun, 130033, Jilin, China.

**RESUMEN / SUMMARY:** - Glioblastoma is the most aggressive cerebral gliomas. Despite advances in therapies, the prognosis is still very poor. Therefore, novel therapeutic strategies are required. As a proteasome inhibitor, bortezomib has shown its efficacy as an active antitumor agent against a variety of tumors. However, inhibition of proteasome activity leads to cell death and also induces cell autophagy, and due to the dual roles of autophagy in the survival and death of tumor cells, the effect of inhibition of autophagy on glioblastoma cells remains to be explored. We therefore assessed whether bortezomib is capable of inducing autophagy, and investigated the antitumor effect of bortezomib combined with autophagy inhibitors on human glioblastoma U251 and U87 cells. Cell viability was measured by MTT assay. The expressions of autophagy and apoptosis-related proteins were determined by Western blot analysis. U251 and U87 cells proliferation was inhibited in a dose-dependent manner. Both apoptosis and autophagy induced by bortezomib were observed in human glioblastoma U87 and U251 cells. However, when U251 and U87 cells were co-treated with bortezomib and autophagy inhibitors 3-MA or Atg7 siRNA, the autophagy inhibitors blocked the autophagy in the cells and resulted in a further inhibition of cell proliferation and a further increase in cell apoptosis as compared with that treated with bortezomib alone. These findings indicated that combination of bortezomib and autophagy inhibitors may shed new light on glioblastoma treatment.

[430]

**TÍTULO / TITLE:** - ERK1/2 inhibition enhances apoptosis induced by JAK2 silencing in human gastric cancer SGC7901 cells.

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

**REVISTA / JOURNAL:** - Mol Cell Biochem. 2013 Nov 1.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1881-6](#)

**AUTORES / AUTHORS:** - Qian C; Yao J; Wang J; Wang L; Xue M; Zhou T; Liu W; Si J

**INSTITUCIÓN / INSTITUTION:** - Institute of Gastroenterology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, 310016, Zhejiang, People's Republic of China.

**RESUMEN / SUMMARY:** - Recent studies suggest JAK2 signaling may be a therapeutic target for treatment of gastric cancer (GC). However, the exact roles of JAK2 in gastric carcinogenesis are not very clear. Here, we have targeted JAK2 to be silenced by shRNA and investigated the biological functions and related mechanisms of JAK2 in GC cell SGC7901. In this study, JAK2 is commonly highly expressed in GC tissues as compared to their adjacent normal tissues (n = 75, p < 0.01). Specific down-regulation of JAK2 suppressed cell proliferation and colony-forming units, induced G2/M arrest in SGC7901 cells, but had no significant effect on cell apoptosis in vitro or tumor growth inhibition in vivo. Interestingly, JAK2 silencing-induced activation of ERK1/2, and inactivation of ERK1/2 using the specific ERK inhibitor PD98059 markedly enhanced JAK2 shRNA-induced cell proliferation inhibition, cell cycle arrest and apoptosis. Ultimately, combination of PD98059 and JAK2 shRNA significantly inhibited tumor growth in nude mice. Our results implicate JAK2 silencing-induced cell proliferation inhibition, cell cycle arrest, and ERK1/2 inhibition could enhance apoptosis induced by JAK2 silencing in SGC7901 cells.

[431]

**TÍTULO / TITLE:** - Inhibition of Six1 promotes apoptosis, suppresses proliferation, and migration of osteosarcoma cells.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 11.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1258-1](#)

**AUTORES / AUTHORS:** - Hua L; Fan L; Aichun W; Yongjin Z; Qingqing C; Xiaojian W

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopedics, Haian Hospital of Traditional Chinese Medicine, 55 Ninghai Middle Road, Haian, 226600, Jiangsu Province, People's Republic of China.

**RESUMEN / SUMMARY:** - Sineoculis homeobox homolog 1 (Six1) is one of the transcription factors that act as master regulators of development and is frequently dysregulated in cancers. However, the biological role of Six1 is not clear in osteosarcoma. To address the expression of Six1 in osteosarcoma cells, three osteosarcoma cell lines (U2OS, SaOS-2, and MG63) and a human osteoblastic cell line (hFOB1.19) were used to detect the expression of Six1 by quantitative real-time polymerase chain reaction and western blotting. The results showed that Six1 was upregulated in osteosarcoma cell lines compared to human osteoblastic cell line hFOB1.19. To investigate the role of Six1 in osteosarcoma cells, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, flow cytometry analysis, and transwell

chamber assays were used to determine the effects of Six1 on the cell viability, cycle, apoptosis, and migration properties in U2OS cells. The results showed that Six1 could promote U2OS cell proliferation and migration, and suppress U2OS cell apoptosis. In addition, we investigated the effects of Six1 on the expression of following proteins (cyclin D1, caspase-3, and vascular endothelial growth factor-C (VEGF-C)). Results showed that Six1 could increase the expression of cyclin D1 and VEGF-C, and decrease the expression of caspase-3. All these data suggested that Six1 might be involved in the promotion of growth, proliferation, and migration of U2OS cells, as well as the inhibition of apoptosis of U2OS cells. These data might provide information for the prediction of osteosarcoma prognosis and potential targets for therapy of osteosarcoma.

[432]

**TÍTULO / TITLE:** - Autocrine production of interleukin-6 confers ovarian cancer cells resistance to tamoxifen via ER isoforms and SRC-1.

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

**REVISTA / JOURNAL:** - Mol Cell Endocrinol. 2013 Nov 1;382(2):791-803. doi: 10.1016/j.mce.2013.10.029.

●● Enlace al texto completo (gratis o de pago) [1016/j.mce.2013.10.029](#)

**AUTORES / AUTHORS:** - Wang Y; Qu Y; Zhang XL; Xing J; Niu XL; Chen X; Li ZM

**INSTITUCIÓN / INSTITUTION:** - Tianjin Key Laboratory for Prevention and Control of Occupational and Environmental Hazard, Tianjin, People's Republic of China; Department of Immunology, Logistics College of Chinese People's Armed Police Forces, Tianjin, People's Republic of China. Electronic address: [wangyue6808@126.com](mailto:wangyue6808@126.com).

**RESUMEN / SUMMARY:** - Although 40-60% of ovarian cancer (OVCA)s express estrogen receptor (ER)alpha, only a minor proportion of patients respond to anti-estrogen treatment with ER antagonist tamoxifen (TAM). The mechanism underlying TAM resistance in the course of OVCA progression is incompletely understood. However, interleukin-6 (IL-6) plays a critical role in the development and progression of OVCA. Here we explore an association between IL-6 and TAM resistance. We demonstrate that both exogenous (a relatively short period of treatment with recombinant IL-6) and endogenous IL-6 (by transfecting with plasmid encoding for sense IL-6) induce TAM resistance in non-IL-6-expressing A2780 cells, while deleting of endogenous IL-6 expression in IL-6-overexpressing CAOV-3 cells (by transfecting with plasmid encoding for antisense IL-6) promotes the sensitivity of these cells to TAM. Further investigation indicates that TAM resistance caused by IL-6 is associated with the alteration of ERalpha, ERbeta and steroid hormone receptor coactivator (SRC)-1 expression levels, the protein interactions between SRC-1 and ERalpha, but not ERbeta, as well as blockage of estrogen-induced ER receptor nuclear translocation. These results show that IL-6 secreted by OVCA cells may contribute to the refractoriness of these cells to TAM via ER isoforms and SRC-1. Overexpression of IL-6 not only plays an important role in OVCA progression but also contributes to TAM resistance. Our studies suggest that TAM-IL-6-targeted adjunctive therapy may lead to a more effective intervention than TAM alone.

[433]

**TÍTULO / TITLE:** - In vitro cytotoxicity on human ovarian cancer cells by T-type calcium channel blockers.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Dec 15;23(24):6656-62. doi: 10.1016/j.bmcl.2013.10.049. Epub 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.10.049](#)

**AUTORES / AUTHORS:** - Jang SJ; Choi HW; Choi DL; Cho S; Rim HK; Choi HE; Kim KS; Huang M; Rhim H; Lee KT; Lee JY

**INSTITUCIÓN / INSTITUTION:** - Research Institute for Basic Sciences and Department of Chemistry, College of Sciences, Kyung Hee University, Seoul 130-701, Republic of Korea.

**RESUMEN / SUMMARY:** - The growth inhibition of human cancer cells via T-type Ca(2+) channel blockade has been well known. Herein, a series of new 3,4-dihydroquinazoline derivatives were synthesized via a brief SAR study on KYS05090 template and evaluated for both T-type Ca(2+) channel (Cav3.1) blockade and cytotoxicity on three human ovarian cancer cells (SK-OV-3, A2780 and A2780-T). Most of compounds except 6i generally exhibited more potent cytotoxicity on SK-OV-3 than mibefradil as a positive control regardless of the degree of T-type channel blockade. In particular, eight compounds (KYS05090, 6a and 6c-6h) showing strong channel blockade exhibited almost equal and more potent cytotoxicity on A2780 when compared to mibefradil. On A2780-T paclitaxel-resistant human ovarian carcinoma, two compounds (KYS05090 and 6d) were 20-fold more active than mibefradil. With respect to cell cycle arrest effect on A2780 and A2780-T cells, KYS05090 induced large proportion of sub-G1 phase in the cell cycle progression of A2780 and A2780-T, meaning the induction of cancer cell death instead of cell cycle arrest via blocking T-type Ca(2+) channel. Among new analogues, compounds 6g and 6h induced cell cycle arrest at G1 phase of A2780 and A2780-T cells in dose-dependent manner and exhibited strong anti-proliferation effects of ovarian cancer cells by blocking T-type Ca(2+) channel. Furthermore, 6g and 6h possessing strong cytotoxic effects could induce apoptosis of A2780 cells, which was detected by confocal micrographs using DAPI staining.

[434]

**TÍTULO / TITLE:** - Genome-wide profiling is a clinically relevant and affordable prognostic test in posterior uveal melanoma.

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

**REVISTA / JOURNAL:** - Br J Ophthalmol. 2013 Oct 29. doi: 10.1136/bjophthalmol-2013-303867.

●● Enlace al texto completo (gratis o de pago) [1136/bjophthalmol-2013-303867](#)

**AUTORES / AUTHORS:** - Cassoux N; Rodrigues MJ; Plancher C; Asselain B; Levy-Gabriel C; Lumbroso-Le Rouic L; Piperno-Neumann S; Dendale R; Sastre X; Desjardins L; Couturier J

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology, Institut Curie 26 rue d'Ulm, Paris, France.

**RESUMEN / SUMMARY:** - OBJECTIVE: This study investigated the capacity of genetic analysis of uveal melanoma samples to identify high-risk patients and discusses its clinical implications. METHODS: Patients with posterior uveal melanoma were prospectively enrolled. Tumour samples were derived from enucleated globe, fine-needle aspirates or endoresection. Chromosome 3 and 8 status was determined by array comparative genomic hybridisation (array-CGH). Patients were followed after treatment to detect metastasis. RESULTS: Four groups were classified by array-CGH. Patients were divided into disomy 3 and normal chromosome 8 (D3/8nl), disomy 3 and 8q gain (D3/8g), monosomy 3 and normal chromosome 8 (M3/8nl) and monosomy 3 and 8 or 8q gain (M3/8g). Median follow-up was 28 months (range: 1-147 months). At the end of the study, 128 patients (33.7%) had developed metastasis and 96 patients had died. Univariate Cox proportional hazard analysis showed that factors associated with metastasis included basal tumour diameter  $p=0.0007$ , tumour thickness  $p=0.01$ , mixed/epithelioid cell type  $p=0.0009$  and genomic data  $p<0.0001$ . High-risk profile was more strongly associated with metastasis than the other prognostic factors  $p<0.001$ . Multivariate Cox modelling analysis showed that the status of chromosomes 3 and 8 were the only two variables that independently contributed to prognosis: monosomy 3 alone  $p=0.001$  and monosomy 3 and 8q gain  $p<0.0001$ . CONCLUSIONS: Array-CGH allowed identification of three prognostic groups with low, intermediate and high risk of developing metastasis. Array-CGH is a reliable and inexpensive method for uveal melanoma prognosis. This method is now currently used in France.

[435]

**TÍTULO / TITLE:** - An Investigation into the Anticancer Effects and Mechanism of Action of Hop beta-Acid Lupulone and Its Natural and Synthetic Derivatives in Prostate Cancer Cells.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Oct;65(7):1086-92. doi: 10.1080/01635581.2013.850963. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.850963](#)

**AUTORES / AUTHORS:** - Mouratidis PX; Colston KW; Tucknott ML; Tyrrell E; Pirianov G

**INSTITUCIÓN / INSTITUTION:** - a Division of Clinical Sciences , St. George's University of London , London , UK.

**RESUMEN / SUMMARY:** - Lupulone, a beta-acid derived from hop extracts has been shown to exhibit antibacterial and anticancer activity. In this study we investigated the anticancer potency of lupulone and its novel derivatives and their mechanism of action on prostate cancer cells. Cell viability was determined using the MTT assay, and the ELISA approach was used to investigate induction of apoptosis. Immunoblot analysis was carried out to determine activation and regulation of proteins associated with cell death. Screening of natural and new lupulone derivatives for their anticancer activity demonstrated that one (lupulone derivative 1h) displayed stronger anticancer activity than lupulone itself on PC3 and DU145 prostate cancer cells. We further found that lupulone derivatives induced caspase-dependent apoptosis that is associated with activation of caspases 8, 9, and 3. Furthermore, caspase 8 inhibitor Z-IETD-fmk reduced cell death induced by lupulone derivatives, suggesting that apoptosis is mediated by caspase 8. Finally, we found that lupulone and its synthetic derivatives

also increased formation of LC3II suggesting that autophagy is also implicated in prostate cancer cell death. The new lupulone derivatives induce caspase-dependent apoptosis and autophagy in prostate cancer cells and appear to be good candidates for further preclinical studies of prostate cancer treatment.

[436]

**TÍTULO / TITLE:** - High ALK mRNA expression has a negative prognostic significance in rhabdomyosarcoma.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 22. doi: 10.1038/bjc.2013.653.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.653](#)

**AUTORES / AUTHORS:** - Bonvini P; Zin A; Alaggio R; Pawel B; Bisogno G; Rosolen A

**INSTITUCIÓN / INSTITUTION:** - 1] Pediatric Onco-Haematology Clinic, University-Hospital of Padova, via Giustiniani 3, 35100 Padova, Italy [2] Institute of Pediatric Research Citta della Speranza, 35100 Padova, Italy.

**RESUMEN / SUMMARY:** - Background: Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase aberrantly expressed in cancer, but its clinical and functional importance remain controversial. Mutation or amplification of ALK, as well as its expression levels assessed by conventional immunohistochemistry methods, has been linked to prognosis in cancer, although with potential bias because of the semi-quantitative approaches. Herein, we measured ALK mRNA expression in rhabdomyosarcoma (RMS) and determined its clinical impact on patients' stratification and outcome. Methods: Specimens were obtained from RMS patients and cell lines, and ALK expression was analysed by quantitative RT-PCR, western blotting, IHC, and copy number analysis. Results: High ALK mRNA expression was detected in the vast majority of PAX3/7-FOXO1-positive tumours, whereas PAX3/7-FOXO1-negative RMS displayed considerably lower amounts of both mRNA and protein. Notably, ALK mRNA distinguished unfavourable PAX3/7-FOXO1-positive tumours from PAX3/7-FOXO1-negative RMS ( $P < 0.0001$ ), and also correlated with larger tumour size ( $P < 0.05$ ) and advanced clinical stage ( $P < 0.01$ ), independently of fusion gene status. High ALK mRNA levels were of prognostic relevance by Cox univariate regression analysis and correlated with increased risk of relapse ( $P = 0.001$ ) and survival ( $P = 0.01$ ), whereas by multivariate analysis elevated ALK mRNA expression resulted a negative prognostic marker when clinical stage was not included. Conclusion: Quantitative assessment of ALK mRNA expression helps to improve risk stratification of RMS patients and identifies tumours with adverse biological characteristics and aggressive behaviour. British Journal of Cancer advance online publication, 22 October 2013; doi:10.1038/bjc.2013.653 [www.bjcancer.com](http://www.bjcancer.com).

[437]

**TÍTULO / TITLE:** - Prognostic factors for locally advanced cervical cancer treated with neoadjuvant intravenous and transarterial chemotherapy followed by radical hysterectomy.

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

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 Oct;23(8):1470-5. doi: 10.1097/IGC.0b013e3182a3402f.

●● Enlace al texto completo (gratis o de pago) [1097/IGC.0b013e3182a3402f](https://doi.org/10.1097/IGC.0b013e3182a3402f)

**AUTORES / AUTHORS:** - Tsubamoto H; Yamamoto S; Kanazawa R; Sakane R; Honda O; Kobayashi K; Shibahara H; Hirota S

**INSTITUCIÓN / INSTITUTION:** - Departments of \*Obstetrics and Gynecology, and daggerRadiology, Hyogo College of Medicine, Hyogo, Japan.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** The aim of this study was to identify prognostic factors associated with neoadjuvant transuterine arterial chemotherapy (TUAC) followed by type III radical hysterectomy. **METHODS:** The medical histories of patients with stage IB2 to IIB cervical cancer who received neoadjuvant TUAC between 1996 and 2009 at our institution were retrospectively reviewed. **RESULTS:** Seventy-three patients received TUAC using cisplatin combined with intravenous nedaplatin, irinotecan, paclitaxel, or etoposide administration. Forty-seven patients (64%) had squamous cell carcinoma. The radiological response rate was 96% (95% confidence interval, 91%-100%). Radical hysterectomy was completed for 95% of enrolled patients. Examination of the resected cervical specimens showed that tumor cells were absent in 19 cases and stromal invasion was less than 3 mm in 7 cases. Among these 26 patients, 23 (32%) had pathologically negative pelvic lymph nodes and no recurrence during the follow-up period. The 5-year relapse-free survival and overall survival rates were 69% and 74%, respectively. Among 23 patients with recurrence or progressive disease, the median survival time after recurrence or progression was 12 months. In multivariate analysis, a tumor size of more than 60 mm and pathological positive lymph nodes were negative prognostic factors for overall survival. **CONCLUSIONS:** Tumor size, pathological response, and lymph node metastases were prognostic factors for cervical cancer. The high pathological response rate associated with TUAC makes it a promising treatment for bulky cervical cancer.

[438]

**TÍTULO / TITLE:** - Mitochondrial translocation of cofilin-1 promotes apoptosis of gastric cancer BGC-823 cells induced by ursolic acid.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1325-7](https://doi.org/10.1007/s13277-013-1325-7)

**AUTORES / AUTHORS:** - Tang Q; Ji Q; Tang Y; Chen T; Pan G; Hu S; Bao Y; Peng W; Yin P

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Laboratories & Experimental Center, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, 200062, China.

**RESUMEN / SUMMARY:** - The pathogenesis of gastric cancer is characterized by excessive proliferation, abnormal differentiation, and reduced apoptosis. Ursolic acid, extracted from traditional Chinese medicine bearberry, inhibits cell growth and induces apoptosis in gastric cancer. However, the mechanism of the proapoptotic effect of ursolic acid on gastric cancer cells needs further investigation. In our present study, we found in apoptotic gastric cancer BGC-823 cells induced by ursolic acid that a translocation of cofilin-1 protein from the cytoplasm to the mitochondria promoted the release of cytochrome c from the mitochondria to the cytoplasm, thereby activating the caspase cascade and finally inducing gastric cancer cell apoptosis. These results implied that the mitochondrial translocation of cofilin-1 might play a crucial role in the

promotion of apoptosis and might be a key target for future treatment of human gastric cancer.

[439]

**TÍTULO / TITLE:** - KIAA0101 mRNA overexpression in peripheral blood mononuclear cells acts as predictive marker for hepatic cancer.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1353-3](#)

**AUTORES / AUTHORS:** - Su X; Zhang T; Cheng P; Zhu Y; Li H; Li D; Liu Z; Gao H; Zhao Z; Zhao Y; Liu H

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Chengdu Military General Hospital, No. 270 Rongdu Road, Chengdu City, Si Chuan Province, 610083, China.

**RESUMEN / SUMMARY:** - KIAA0101 always overexpresses in tumor tissues, which is also a marker of tumor recurrence. This study aims to explore whether overexpression of KIAA0101 mRNA in peripheral blood mononuclear cells (PBMCs) could act as a noninvasive and predictive biomarker of hepatic cancer. Real-time polymerase chain reaction (RT-PCR) was employed to detect KIAA0101 mRNA expression in PBMCs isolated from 93 hepatic cancer patients and 55 healthy individuals. The diagnostic sensitivity and specificity of KIAA0101 mRNA, CEA, and CD44V were analyzed and compared. A multivariate logistic regression analysis was utilized to analyze risk factors for overall survival of hepatic cancer patients. A concordance analysis was employed to compare the overexpression of KIAA0101 mRNA with clinicopathological diagnosis. All of the 93 hepatic cancer patients were followed up routinely at least 36 months or until death to analyze the 3-year overall survival rate. The results indicated that KIAA0101 mRNA expression was increased significantly in hepatic patients' PBMCs, when compared with that of healthy individuals ( $P < 0.05$ ). Both the sensitivity and specificity of KIAA0101 mRNA in PBMCs were enhanced significantly compared with those of the CEA and CD44V biomarkers. The multivariate logistic regression analysis indicated that the KIAA0101 mRNA level and pTNM stage were significantly related with the overall survival of the hepatic patients. There was a better concordance between KIAA0101 mRNA overexpression and clinicopathological diagnosis for hepatic cancer ( $\kappa = 0.914$ ,  $P < 0.001$ ). KIAA0101 mRNA overexpression in PBMCs decreased the 3-year survival rate significantly. In conclusion, overexpression of KIAA0101 mRNA in PBMCs could act as a predictive biomarker for hepatic cancer and has a better sensitivity and specificity.

[440]

**TÍTULO / TITLE:** - Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells.

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

**REVISTA / JOURNAL:** - Brain Behav Immun. 2013 Nov 5. pii: S0889-1591(13)00529-1. doi: 10.1016/j.bbi.2013.10.030.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbi.2013.10.030](#)

**AUTORES / AUTHORS:** - Bigley AB; Rezvani K; Chew C; Sekine T; Pistillo M; Crucian B; Bollard CM; Simpson RJ

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Integrated Physiology, Department of Health and Human Performance, University of Houston, 3855 Holman Street, Houston, TX 77204, USA. Electronic address: [abbigley@uh.edu](mailto:abbigley@uh.edu).

**RESUMEN / SUMMARY:** - NK-cells undergo a “licensing” process as they develop into fully-functional cells capable of efficiently killing targets. NK-cell differentiation is accompanied by an increased surface expression of inhibitory killer immunoglobulin-like receptor (KIR) molecules, which is positively associated with cytotoxicity against the HLA-deficient K562 cell line. NK-cells are rapidly redeployed between the blood and tissues in response to acute exercise, but it is not known if exercise evokes a preferential trafficking of differentiated NK-cells or impacts NK-cell cytotoxic activity (NKCA) against HLA-expressing target cells. Sixteen healthy cyclists performed three 30-min bouts of cycling exercise at -5%, +5%, and +15% of lactate threshold. Blood samples obtained before, immediately after, and 1h after exercise were used to enumerate NK-cells and their subsets, and determine NKCA and degranulating subsets (CD107+) against cell lines of multiple myeloma (U266 and RPMI-8226), lymphoma (721.221 and 221 AEH), and leukemia (K562) origin by 4 and 11-color flow cytometry, respectively. Exercise evoked a stepwise redeployment of NK-cell subsets in accordance with differentiation status [highly-differentiated (KIR+/NKG2A-) >medium-differentiated (KIR+/NKG2A+)>low-differentiated (KIR-/NKG2A+)] that was consistent across all exercise intensities. NKCA per cell increased approximately 1.6-fold against U266 and 221 AEH targets 1h post-exercise and was associated with a decreased proportion of NK-cells expressing the inhibitory receptor CD158b and increased proportion of NK-cells expressing the activating receptor NKG2C, respectively. We conclude that exercise evokes a preferential redeployment of NK-cell subsets with a high differentiation phenotype and augments cytotoxicity against HLA-expressing target cells. Exercise may serve as a simple strategy to enrich the blood compartment of highly cytotoxic NK-cell subsets that can be harvested for clinical use.

[441]

**TÍTULO / TITLE:** - Oxime-based inhibitors of glucose transporter 1 displaying antiproliferative effects in cancer cells.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Dec 15;23(24):6923-7. doi: 10.1016/j.bmcl.2013.09.037. Epub 2013 Sep 28.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.09.037](http://1016/j.bmcl.2013.09.037)

**AUTORES / AUTHORS:** - Tuccinardi T; Granchi C; Iegre J; Paterni I; Bertini S; Macchia M; Martinelli A; Qian Y; Chen X; Minutolo F

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Farmacia, Università di Pisa, Via Bonanno 6, 56126 Pisa, Italy.

**RESUMEN / SUMMARY:** - An analysis of the main pharmacophoric features present in the still limited number of inhibitors of glucose transporter GLUT1 led to the identification of new oxime-based inhibitors, which proved to be able to efficiently hinder glucose uptake and cell growth in H1299 lung cancer cells. The most important interactions of a representative inhibitor were indicated by a novel computational model of GLUT1, which was purposely developed to explain these results and to provide

useful indications for the design and the development of new and more efficient GLUT1 inhibitors.

[442]

**TÍTULO / TITLE:** - Neobavaisoflavone sensitizes apoptosis via the inhibition of metastasis in TRAIL-resistant human glioma U373MG cells.

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

**REVISTA / JOURNAL:** - Life Sci. 2013 Nov 11. pii: S0024-3205(13)00682-6. doi: 10.1016/j.lfs.2013.10.035.

●● Enlace al texto completo (gratis o de pago) [1016/j.lfs.2013.10.035](#)

**AUTORES / AUTHORS:** - Kim YJ; Choi WI; Ko H; So Y; Kang KS; Kim I; Kim K; Yoon HG; Kim TJ; Choi KC

**INSTITUCIÓN / INSTITUTION:** - Natural Medicine Center, Korea Institute of Science and Technology, Gangneung, Gangwon-do, South Korea.

**RESUMEN / SUMMARY:** - AIMS: Neobavaisoflavone (NBIF), an isoflavone isolated from *Psoralea corylifolia* (Leguminosae), has striking anti-inflammatory and anti-cancer effects. NBIF inhibits the proliferation of prostate cancer in vitro and in vivo. MAIN METHODS: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a key endogenous molecule that selectively induces apoptosis in cancer cells with little or no toxicity in normal cells. However, some cancer cells, including U373MG cells, are resistant to TRAIL-mediated apoptosis. We demonstrated that the cell viability, migration and invasion assay were used in U373MG glioma cells. KEY FINDINGS: In this study, we found that NBIF sensitizes human U373MG glioma cells to TRAIL-mediated apoptosis. Co-treatment of TRAIL and NBIF effectively induced Bid cleavage and activated caspases 3, 8, and 9. Importantly, DR5 expression was upregulated by NBIF. We also observed that the combination NBIF and TRAIL increased expression of BAX. We further demonstrate that NBIF induced TRAIL-mediated apoptosis in human glioma cells by suppressing migration and invasion, and by inhibiting anoikis resistance. SIGNIFICANCE: Taken together, our results suggest that NBIF reduces the resistance of cancer cells to TRAIL and that the combination of NBIF and TRAIL may be a new therapeutic strategy for treating TRAIL-resistant glioma cells.

[443]

**TÍTULO / TITLE:** - MicroRNA-31 inhibits cisplatin-induced apoptosis in non-small cell lung cancer cells by regulating the drug transporter ABCB9.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Oct 4. pii: S0304-3835(13)00703-9. doi: 10.1016/j.canlet.2013.09.034.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.09.034](#)

**AUTORES / AUTHORS:** - Dong Z; Zhong Z; Yang L; Wang S; Gong Z

**INSTITUCIÓN / INSTITUTION:** - Institute of Biochemistry and Molecular Biology, Zhejiang Provincial Key Laboratory of Pathophysiology, Ningbo University School of Medicine, Ningbo, China.

**RESUMEN / SUMMARY:** - Alterations in microRNA (miRNA) expression have been found to be involved in tumor growth and response to chemotherapy. However, the possible role of miR-31 in cisplatin (DDP) resistance in non-small cell lung cancer

(NSCLC) remains unclear. In this study, we identified a DDP-sensitive and a DDP-resistant cell line from four candidate human NSCLC cell lines. Notably, we found that miR-31 was significantly upregulated in the DDP-resistant cell line compared with its level in the DDP-sensitive cell line. As a result, miR-31 overexpression induced DDP resistance in the DDP-sensitive cell line, and miR-31 knockdown rescued DDP sensitivity in the DDP-resistant cell line. Interestingly, miR-31 was inversely correlated with the expression of the drug resistance gene ABCB9. The luciferase activity assay showed that miR-31 directly targets the 3'UTR of ABCB9, which is known to play a crucial role in drug resistance. Mechanistically, we showed that miR-31 confers DDP-induced apoptosis and that inhibition of ABCB9 is required for DDP resistance. The data demonstrate that miR-31 exerts an anti-apoptotic effect most likely through the inhibition of ABCB9 and thus provide a novel strategy involving the use of miR-31 as a potential target in NSCLC chemotherapy.

[444]

**TÍTULO / TITLE:** - 5'-Triphosphate-siRNA activates RIG-I-dependent type I interferon production and enhances inhibition of hepatitis B virus replication in HepG2.2.15 cells.

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

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 Dec 5;721(1-3):86-95. doi: 10.1016/j.ejphar.2013.09.050. Epub 2013 Oct 5.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejphar.2013.09.050](#)

**AUTORES / AUTHORS:** - Chen X; Qian Y; Yan F; Tu J; Yang X; Xing Y; Chen Z

**INSTITUCIÓN / INSTITUTION:** - Division of Infection and Immunity, Department of Electromagnetic and Laser Biology, Beijing Institute of Radiation Medicine, 27 Taiping Rd, Beijing 100850, China.

**RESUMEN / SUMMARY:** - Hepatitis B virus (HBV) infection often results in acute or chronic viral hepatitis and other liver diseases including cirrhosis and hepatocellular carcinoma. Current therapies for HBV usually have severe side effects and can cause development of drug-resistant mutants. An alternative and safe immunotherapeutic approach for HBV infection is urgently needed for effective anti-HBV therapy. In this study, we propose a new strategy for anti-HBV therapy that activates type-I interferon (IFN) antiviral innate immunity through stimulating pattern-recognition receptors with RNA interference (RNAi) using a 5'-end triphosphate-modified small interfering RNA (3p-siRNA). We designed and generated a 3p-siRNA targeting overlapping region of S gene and P gene of the HBV genome at the 5'-end of pregenomic HBV RNA. Our results demonstrated that 3p-siRNA induced a RIG-I-dependent antiviral type-I IFN response when transfected into HepG2.2.15 cells that support HBV replication. The 3p-siRNA significantly inhibited HBsAg and HBeAg secretion from HepG2.2.15 cells in a RIG-I-dependent manner, and the antiviral effect of 3p-siRNA was superior to that of siRNA. Furthermore, 3p-siRNA had more pronounced inhibition effects on the replication of HBV DNA and the transcription of mRNA than that of siRNA. Finally, 3p-siRNA displayed antiviral activity with long-term suppression of HBV replication. In conclusion, our findings suggest that 3p-siRNA could act as a powerful bifunctional antiviral molecule with potential for developing a promising therapeutic against chronic HBV infection.

[445]

**TÍTULO / TITLE:** - Oxymatrine induces mitochondria dependent apoptosis in human osteosarcoma MNNG/HOS cells through inhibition of PI3K/Akt pathway.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Sep 29.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1223-z](#)

**AUTORES / AUTHORS:** - Zhang Y; Sun S; Chen J; Ren P; Hu Y; Cao Z; Sun H; Ding Y  
**INSTITUCIÓN / INSTITUTION:** - Institute of Osteosarcoma, Tangdu Hospital of the Fourth Military Medical University, 1 Xinsi Road, Xi'an, Shaanxi, 710038, China.

**RESUMEN / SUMMARY:** - The cytostatic drug from traditional Chinese medicinal herb has acted as a chemotherapeutic agent used in treatment of a wide variety of cancers. Oxymatrine, classified as a quinolizidine alkaloid, is a phytochemical product derived from *Sophora flavescens*, and has been reported to possess anticancer activities. However, the cancer growth inhibitory effects and molecular mechanisms in human osteosarcoma MNNG/HOS cell have not been well studied. In the present study, the cytotoxic effects of oxymatrine on MNNG/HOS cells were examined by MTT and bromodeoxyuridine (BrdU) incorporation assays. The percentage of apoptotic cells and the level of mitochondrial membrane potential ( $\Delta\psi_m$ ) were assayed by flow cytometry. The levels of apoptosis-related proteins were measured by Western blot analysis or enzyme assay Kit. Our results showed that treatment with oxymatrine resulted in a significant inhibition of cell proliferation and DNA synthesis in a dose-dependent manner, which has been attributed to apoptosis. Furthermore, we found that oxymatrine considerably inhibited the expression of Bcl-2 whilst increasing that of Bax. This promoted mitochondrial dysfunction, leading to the release of cytochrome c from the mitochondria to the cytoplasm, as well as the activation of caspase-9 and -3. Moreover, addition of oxymatrine to MNNG/HOS cells also attenuated phosphatidylinositol 3-kinase (PI3K) Akt signaling pathway cascade, evidenced by the dephosphorylation of P13K and Akt. Likewise, oxymatrine significantly suppressed tumor growth in female BALB/C nude mice bearing MNNG/HOS xenograft tumors. In addition, no evidence of drug-related toxicity was identified in the treated animals by comparing the body weight increase and mortality. Therefore, these findings should be useful for understanding the apoptotic cellular mechanism mediated by oxymatrine and might offer a therapeutic potential advantage for human osteosarcoma chemoprevention or chemotherapy.

[446]

**TÍTULO / TITLE:** - Anti-hepatoma cells function of luteolin through inducing apoptosis and cell cycle arrest.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 28.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1396-5](#)

**AUTORES / AUTHORS:** - Ding S; Hu A; Hu Y; Ma J; Weng P; Dai J

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, The Affiliated Ningbo No.2 Hospital, College of Medicine, Ningbo University, Ningbo, Zhejiang, 315010, China.

**RESUMEN / SUMMARY:** - The aim of this study is to explore the apoptotic induction and cell cycle arrest function of luteolin on the liver cancer cells and the related mechanism.

The liver cancer cell line SMMC-7721, BEL-7402, and normal liver cells HL-7702 were treated with different concentrations of luteolin. Cell proliferation ability was tested. Morphological changes of the apoptotic cells were observed under inverted fluorescence microscope after Hoechst33342 staining. We investigated the effect of luteolin on cell cycling and apoptosis with flow cytometry. The mitochondrial membrane potential changes were analyzed after JC-1 staining. Caspases-3 and Bcl-2 family proteins expression were analyzed by real-time PCR. Cell proliferation of SMMC-7721 and BEL-7402 were inhibited by luteolin, and the inhibition was dose-time-dependent. Luteolin could arrest the cells at G1/S stage, reduce mitochondrial membrane potential, and induce higher apoptosis rate and the typical apoptotic morphological changes of the liver carcinoma cells. Q-RT-PCR results also showed that luteolin increased Bax and caspase-3 expression significantly and upregulated Bcl-2 expression in a dose-dependent manner in liver carcinoma cells. However, the normal liver cells HL-7702 was almost not affected by luteolin treatment. Luteolin can inhibit SMMC-7721 and BEL-7402 cell proliferation in a time- and dose-dependent manner. And the mechanism maybe through arresting cell cycle at phase G1/S, enhancing Bax level, reducing anti-apoptotic protein Bcl-2 level, resulting in activating caspase-3 enzyme and decrease of mitochondrial membrane potential, and finally leading to cell apoptosis.

[447]

**TÍTULO / TITLE:** - Bufalin exerts antitumor effects by inducing cell cycle arrest and triggering apoptosis in pancreatic cancer cells.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1326-6](#)

**AUTORES / AUTHORS:** - Li M; Yu X; Guo H; Sun L; Wang A; Liu Q; Wang X; Li J

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Cancer Center, Qilu Hospital, Shandong University, Jinan, 250012, China.

**RESUMEN / SUMMARY:** - As one of the most aggressive human malignancies, pancreatic cancer is a leading cause of cancer-related deaths worldwide and only about 4 % of patients will live 5 years after diagnosis. Eighty to approximately eighty-five percent of patients are diagnosed with an unresectable or metastatic disease, which is correlated with poor prognosis and low survival rate. Therefore, it is tremendously significant to exploit novel chemicals to prevent and treat pancreatic cancer. Previous research and clinical studies have demonstrated that many natural products derived from traditional Chinese medicine (TCM) such as camptothecin derivatives and vinca alkaloids could be effective antitumor compounds, hinting that TCM is a promising source for developing new antitumor drugs. In this report, we investigated the effects of bufalin, a primary active ingredient of the traditional Chinese medicine Chan-Su, on pancreatic cancer cell lines PANC-1 and CFPAC-1 and studied the underlying molecular mechanism. We found that exposure to bufalin could suppress the proliferation of pancreatic cancer cells time and dose dependently. We used flow cytometry to study the effects of bufalin on apoptosis and cell cycle distribution in PANC-1 and CFPAC-1 cells. The results indicated that bufalin could significantly induce both apoptosis and G2/M cell cycle arrest in pancreatic cancer cells. With western blotting, we found that the expression level of an antiapoptotic

protein heat shock protein 27 (Hsp27) and its partner molecule p-Akt was decreased upon the treatment with bufalin. Besides, bufalin activated pro-caspase-3 and pro-caspase-9 and modulated the expression level of Bcl-2 and Bax. These data suggested that bufalin may trigger apoptosis by targeting Hsp27, which could inhibit apoptosis by interfering with key apoptotic proteins. The influence on the level of cyclinB1, CDK1, and p21 was also observed after bufalin treatment, and the relationship between Hsp27 and the cell cycle-related proteins mentioned above deserves much more research. In addition, our data showed that bufalin could enhance the growth inhibition effect of gemcitabine in above pancreatic cancer cells. Taken together, bufalin might be worthy of further study for its potential as a therapeutic agent for pancreatic cancer treatment.

[448]

**TÍTULO / TITLE:** - The apoptotic effect of shikonin on human papillary thyroid carcinoma cells through mitochondrial pathway.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 2.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1238-5](#)

**AUTORES / AUTHORS:** - Liu C; Yin L; Chen J; Chen J

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Laboratory, Taizhou Municipal Hospital, Taizhou, Zhejiang, 317000, China.

**RESUMEN / SUMMARY:** - This study aims to explore the apoptotic function of shikonin on the papillary thyroid cancer cells and the related mechanism. The papillary thyroid cancer cell lines K1 and W3 and thyroid follicular epithelial cells NTHY-ORI 3-1 were treated with different concentrations of shikonin. Cell proliferation was tested. Morphological changes of the apoptotic cells were observed by Hoechst 33342 staining. The apoptosis rate of the papillary thyroid cancer cells was measured with flow cytometry. Changes of the cell cycle were explored. The mitochondrial membrane potential changes were analyzed after JC-1 staining. Bcl-2 family proteins and caspase-3 expression with shikonin treatment was analyzed by real-time fluorescence polymerase chain reaction (PCR). Cell proliferation of K1 and W3 was inhibited by shikonin, and the inhibition was dose-time dependent. Papillary thyroid carcinoma cells treated by shikonin had no obvious cell cycle arrest but were observed with the higher apoptosis rate and the typical apoptotic morphological changes of the cell nucleus. JC-1 staining showed that shikonin reduced the mitochondrial membrane potential of papillary thyroid carcinoma cells. Real-time PCR results showed that shikonin significantly increased Bax and caspase-3 expression and upregulated Bcl-2 expression in a dose-dependent manner in papillary thyroid carcinoma cells. However, the NTHY-ORI 3-1 was almost not affected by shikonin treatment. Shikonin can inhibit K1 and W3 cell proliferation in a dose- and time-dependent manner, enhance Bax levels, reduce anti-apoptotic protein Bcl-2 levels, result in decreasing mitochondrial membrane potential and activating caspase-3 enzyme, and finally lead to apoptosis.

[449]

**TÍTULO / TITLE:** - Disodium pentaborate decahydrate (DPD) induced apoptosis by decreasing hTERT enzyme activity and disrupting F-actin organization of prostate cancer cells.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1212-2](#)

**AUTORES / AUTHORS:** - Korkmaz M; Avci CB; Gunduz C; Aygunes D; Erbaykent-Tepedelen B

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Biology, Faculty of Medicine, Celal Bayar University, Manisa, 45030, Turkey, [mehmet.korkmaz@cbu.edu.tr](mailto:mehmet.korkmaz@cbu.edu.tr).

**RESUMEN / SUMMARY:** - Animal and cell culture studies have showed that boron and its derivatives may be promising anticancer agents in prostate cancer treatment. Thus, DU145 cells were treated with disodium pentaborate decahydrate (DPD) for 24, 48, and 72 h in order to investigate the inhibitor effect and mechanisms of DPD. Then, cell proliferation, telomerase enzyme activity, actin polymerization, and apoptosis were detected by WST-1 assay, qRT-PCR, immunofluorescence labeling, and flow cytometry, respectively. We found that DPD inhibited the growth of human prostate cancer cell line DU145 at the concentration of 3.5 mM for 24 h. Our results demonstrated that 7 mM of DPD treatment prevented the telomerase enzyme activity at the rate of 38 %. Furthermore, DPD has an apoptotic effect on DU145 cells which were examined by labeling DNA breaks. With 7 mM of DPD treatment, 8, 14, and 41 % of apoptotic cells were detected for 24, 48, and 72 h, respectively. Additionally, immunofluorescence labeling showed that the normal organization of actin filaments was disrupted in DPD-exposed cells, which is accompanied by the alteration of cell shape and by apoptosis in targeted cells. Taken together, the results indicate that DPD may exert its cytotoxicity at least partly by interfering with the dynamic properties of actin polymerization and decreasing the telomerase activity. Eventually, for the first time, the results of this study showed that DPD suppressed the activity of telomerase in DU145 cells, and therefore, we suggested that DPD could be an important agent for its therapeutic potential in the treatment of prostate cancer.

[450]

**TÍTULO / TITLE:** - Induction of apoptosis by total flavonoids from *Scutellaria barbata* D. Don in human hepatocarcinoma MHCC97-H cells via the mitochondrial pathway.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1336-4](#)

**AUTORES / AUTHORS:** - Gao J; Lu WF; Dai ZJ; Lin S; Zhao Y; Li S; Zhao NN; Wang XJ; Kang HF; Ma XB; Zhang WG

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710004, China.

**RESUMEN / SUMMARY:** - *Scutellaria barbata* D. Don, a traditional Chinese medicine, reportedly possesses antitumor activity against a variety of tumors. In the present study, we investigated the cytotoxic effect of total flavonoids from *S. barbata* (TF-SB) on human hepatocarcinoma cells and the underlying molecular mechanisms regarding the effect were explored. TF-SB treatment significantly reduced the cell viability of human HCC MHCC97-H cells in a dose-dependent manner. Further flow cytometric

analysis showed that the apoptosis rate of MHCC97-H cells increased and the mitochondrial membrane potential (psim) of MHCC97-H cells decreased after TF-SB treatment. DNA ladder showed that TF-SB induced a significant increase in DNA fragmentation in MHCC97-H cells. Reverse transcription PCR and Western blot analysis revealed that the expression levels of Smac, Apaf-1, Cytochrome c, Caspase-9, and Caspase-3 were upregulated in a dose-dependent manner and after treatment with different concentrations of TF-SB for 48 h. These results suggest that TF-SB induces apoptosis in MHCC97-H cells through the mitochondrial pathway.

[451]

**TÍTULO / TITLE:** - Familial CD3+ T Large Granular Lymphocyte Leukemia: Evidence that Genetic Predisposition and Antigen Selection Promote Clonal Cytotoxic T-Cell Responses.

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

**REVISTA / JOURNAL:** - Leuk Lymphoma. 2013 Nov 3.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.861065](#)

**AUTORES / AUTHORS:** - Stalika E; Papalexandri A; Iskas M; Stavroyianni N; Kanellis G; Kotta K; Pontikoglou C; Siorenta A; Anagnostopoulos A; Papadaki H; Papadaki T; Stamatopoulos K

**RESUMEN / SUMMARY:** - ABSTRACT CD3+ T-large granular lymphocyte (T-LGL) proliferations often present with cytopenias and splenomegaly and are linked to autoimmunity, especially rheumatoid arthritis and Felty's syndrome. We report here intra-family occurrence of T-LGL leukemia in a father and a son, both presenting with cytopenias and splenomegaly. Both patients carried the HLA-DRB1\*04 allele, strongly associated with rheumatoid arthritis and Felty's syndrome, exhibited distinctive histopathological features suggestive of immune-mediated suppression of hematopoiesis and expressed a remarkably skewed T-cell receptor beta chain gene repertoire with overtime evolution (clonal drift). Immunoinformatics analysis and comparisons with clonotype sequences from various entities revealed (quasi)identities between (i) father and son; and, (ii) father or son and patients with autoimmune disorders, T-LGL leukemia or chronic idiopathic neutropenia. Altogether, our results further corroborate antigen selection in the ontogeny of T-LGL leukemia and point to the interplay between genetics and (micro)environment in shaping the outcome of cytotoxic T cell responses.

[452]

**TÍTULO / TITLE:** - The activation of p38 and JNK by ROS, contribute to OLO-2-mediated intrinsic apoptosis in human hepatocellular carcinoma cells.

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

**REVISTA / JOURNAL:** - Food Chem Toxicol. 2013 Nov 5;63C:38-47. doi: 10.1016/j.fct.2013.10.043.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.10.043](#)

**AUTORES / AUTHORS:** - Zhang Z; Zhang C; Ding Y; Zhao Q; Yang L; Ling J; Liu L; Ji H; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, PR China; School of Life Science and Technology, China Pharmaceutical University, Nanjing 210009, PR China.

**RESUMEN / SUMMARY:** - In this study, we describe that a novel synthesized compound, olean-28,13beta-olide 2 (OLO-2), exhibits selective cytotoxic activity via inducing apoptosis in human hepatocellular carcinoma (HCC) cell lines but not normal human hepatic cells in vitro. Exposure of human HCC HepG2 cells to OLO-2 results in significant loss of mitochondrial transmembrane potential (DeltaPsi<sub>m</sub>), the release of cytochrome c, the recruitment of B-cell lymphoma 2 (Bcl-2) associated X protein (Bax) and the downregulation of Bcl-2. The apoptosis induced by OLO-2 is associated with the activation of caspase-3/9 and the nuclear translocation of apoptosis inducing factor (AIF). Moreover, the increase of phosphorylated p38 and c-Jun N-terminal kinase (JNK) is observed. OLO-2-induced the externalization of phosphatidyl-serine (PS) and the loss of DeltaPsi<sub>m</sub> are blocked by p38 inhibitor SB203580 or JNK inhibitor SP600125. In addition, OLO-2 provokes the generation of reactive oxygen species (ROS) in HepG2 cells, while the antioxidant N-acetyl cysteine (NAC) almost completely blocks OLO-2-induced apoptosis and the activation of p38 and JNK. Taken together, the present study demonstrates that OLO-2 exhibits its cytotoxic activity through intrinsic apoptosis via ROS generation and the activation of p38 and JNK. Its potential to be a candidate of anti-cancer agent is worth being further investigated.

[453]

**TÍTULO / TITLE:** - Smac mimetic primes apoptosis-resistant acute myeloid leukaemia cells for cytarabine-induced cell death by triggering necroptosis.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Oct 30. pii: S0304-3835(13)00747-7. doi: 10.1016/j.canlet.2013.10.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.10.018](http://1016/j.canlet.2013.10.018)

**AUTORES / AUTHORS:** - Chromik J; Safferthal C; Serve H; Fulda S

**INSTITUCIÓN / INSTITUTION:** - Institute for Experimental Cancer Research in Pediatrics, Goethe-University, Frankfurt, Germany; Department of Medicine, Hematology/Oncology, Goethe-University, Frankfurt, Germany.

**RESUMEN / SUMMARY:** - The prognosis for patients with acute myeloid leukaemia (AML) is still poor, thus calling for novel treatment strategies. Here, we report that the small-molecule Smac mimetic BV6, which antagonizes Inhibitor of Apoptosis (IAP) proteins, acts in concert with cytarabine (AraC) to trigger cell death in AML cells in a highly synergistic manner (combination index 0.02-0.27). Similarly, BV6 cooperates with AraC to trigger cell death in primary AML samples, underscoring the clinical relevance of our findings. Molecular studies reveal that the TNFalpha-blocking antibody Enbrel significantly reduces BV6/AraC-induced cell death, demonstrating that an autocrine/paracrine TNFalpha loop mediates cell death. Furthermore, BV6 and AraC synergize to induce loss of mitochondrial membrane potential, caspase activation and DNA fragmentation, consistent with apoptotic cell death. Nevertheless, the caspase inhibitor zVAD.fmk fails to protect against BV6/AraC-induced cell death. Intriguingly, this cell death upon caspase inhibition is significantly reduced by pharmacological inhibition of two key components of necroptosis signaling, i.e. by RIP1 kinase inhibitor Necrostatin-1 or MLKL inhibitor NSA. Thus, BV6 sensitizes AML cells to AraC-induced

cell death and overcomes apoptosis resistance by triggering necroptosis as alternative form of cell death. These findings have important implications for Smac mimetic-based strategies to bypass apoptosis resistance of AML.

[454]

**TÍTULO / TITLE:** - Plumbagin induces apoptotic and autophagic cell death through inhibition of the PI3K/Akt/mTOR pathway in human non-small cell lung cancer cells.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Nov 23. pii: S0304-3835(13)00803-3. doi: 10.1016/j.canlet.2013.11.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.11.001](#)

**AUTORES / AUTHORS:** - Li YC; He SM; He ZX; Li M; Yang Y; Pang JX; Zhang X; Chow K; Zhou Q; Duan W; Zhou ZW; Yang T; Huang GH; Liu A; Qiu JX; Liu JP; Zhou SF

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Xiaolan Hospital, Southern Medical University, Zhongshan, Guangdong 528415, China; Department of Pharmaceutical Science, College of Pharmacy, University of South Florida, Tampa, FL 33612, USA.

**RESUMEN / SUMMARY:** - Plumbagin (PLB) has shown anti-cancer activity but the mechanism is unclear. This study has found that PLB has a potent pro-apoptotic and pro-autophagic effect on A549 and H23 cells. PLB arrests cells in G2/M phase, and increases the intracellular level of reactive oxygen species in both cell lines. PLB dose-dependently induces autophagy through inhibition of PI3K/Akt/mTOR pathway as indicated by reduced phosphorylation of Akt and mTOR. Inhibition or induction of autophagy enhances PLB-induced apoptosis. There is crosstalk between PLB-induced apoptosis and autophagy. These findings indicate that PLB initiates both apoptosis and autophagy in NSCLC cells through coordinated pathways.

[455]

**TÍTULO / TITLE:** - Treatment of Advanced Cutaneous Squamous Cell Carcinomas with Epidermal Growth Factor Receptor Inhibitors.

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

**REVISTA / JOURNAL:** - Dermatology. 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1159/000355181](#)

**AUTORES / AUTHORS:** - Alter M; Satzger I; Mattern A; Kapp A; Gutzmer R

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology and Allergy, Hannover Medical School, Skin Cancer Center Hannover, Hannover, Germany.

**RESUMEN / SUMMARY:** - In advanced cutaneous squamous cell carcinoma (cSCC), efficient medical treatment options are limited in case surgery and radiotherapy failed, particularly since most patients are of higher age and suffer from comorbidities. In many tumor entities, the epidermal growth factor receptor (EGFR) has been established as an important therapeutic target, and blockade of EGFR signaling by monoclonal antibodies or small molecules achieves a therapeutic benefit. EGFR expression is also often dysregulated in cSCC. We report here two patients with advanced cSCC treated with the EGFR inhibitor cetuximab and summarize the current

published experience with the use of EGFR inhibitors in cSCC. © 2013 S. Karger AG, Basel.

[456]

**TÍTULO / TITLE:** - AMG 900, pan-Aurora kinase inhibitor, preferentially inhibits the proliferation of breast cancer cell lines with dysfunctional p53.

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

**REVISTA / JOURNAL:** - Breast Cancer Res Treat. 2013 Oct;141(3):397-408. doi: 10.1007/s10549-013-2702-z. Epub 2013 Oct 5.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2702-z](#)

**AUTORES / AUTHORS:** - Kalous O; Conklin D; Desai AJ; Dering J; Goldstein J; Ginther C; Anderson L; Lu M; Kolarova T; Eckardt MA; Langerod A; Borresen-Dale AL; Slamon DJ; Finn RS

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology/Oncology, Department of Medicine, Geffen School of Medicine at UCLA, 10833 Le Conte Ave, 11-934 Factor Bldg, Los Angeles, CA, 90095, USA.

**RESUMEN / SUMMARY:** - Aurora kinases play important roles in cell division and are frequently overexpressed in human cancer. AMG 900 is a novel pan-Aurora kinase inhibitor currently being tested in Phase I clinical trials. We aimed to evaluate the in vitro activity of AMG 900 in a panel of 44 human breast cancer and immortalized cell lines and identify predictors of response. AMG 900 inhibited proliferation at low nanomolar concentrations in all cell lines tested. Response was further classified based on the induction of lethality. 25 cell lines were classified as highly sensitive (lethality at 10 nM of AMG 900 >10 %), 19 cell lines as less sensitive to AMG 900 (lethality at 10 nM of AMG 900 <10 %). Traditional molecular subtypes of breast cancer did not predict for this differential response. There was a weak association between AURKA amplification and response to AMG 900 (response ratio = 2.53, p = 0.09). mRNA expression levels of AURKA, AURKB, and AURKC and baseline protein levels of Aurora kinases A and B did not significantly associate with response. Cell lines with TP53 loss of function mutations (RR = 1.86, p = 0.004) and low baseline p21 protein levels (RR = 2.28, p = 0.0004) were far more likely to be classified as highly sensitive to AMG 900. AMG 900 induced p53 and p21 protein expression in cell lines with wt TP53. AMG 900 caused the accumulation of cells with >4 N DNA content in a majority of cell lines independently of sensitivity and p53 status. AMG 900 induced more pronounced apoptosis in highly sensitive p53-dysfunctional cell lines. We have found that AMG 900 is highly active in breast cancer cell lines and that TP53 loss of function mutations as well as low baseline expression of p21 protein predict strongly for increased sensitivity to this compound in vitro.

[457]

**TÍTULO / TITLE:** - Amplification of PVT-1 is involved in poor prognosis via apoptosis inhibition in colorectal cancers.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 5. doi: 10.1038/bjc.2013.698.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.698](#)

**AUTORES / AUTHORS:** - Takahashi Y; Sawada G; Kurashige J; Uchi R; Matsumura T; Ueo H; Takano Y; Eguchi H; Sudo T; Sugimachi K; Yamamoto H; Doki Y; Mori M; Mimori K

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Surgery, Kyushu University Beppu Hospital, Tsurumihara 4546, Beppu 874-0838, Japan [2] Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita 565-0871, Japan.

**RESUMEN / SUMMARY:** - Background:We previously conducted gene expression microarray analyses to identify novel indicators for colorectal cancer (CRC) metastasis and prognosis from which we identified PVT-1 as a candidate gene. PVT-1, which encodes a long noncoding RNA, mapped to chromosome 8q24 whose copy-number amplification is one of the most frequent events in a wide variety of malignant diseases. However, PVT-1 molecular mechanism of action remains unclear.Methods:We conducted cell proliferation and invasion assays using colorectal cancer cell lines transfected with PVT-1siRNA or negative control siRNA. Gene expression microarray analyses on these cell lines were also carried out to investigate the molecular function of PVT-1. Further, we investigated the impact of PVT-1 expression on the prognosis of 164 colorectal cancer patients by qRT-PCR.Results:CRC cells transfected with PVT-1 siRNA exhibited significant loss of their proliferation and invasion capabilities. In these cells, the TGF-beta signalling pathway and apoptotic signals were significantly activated. In addition, univariate and multivariate analysis revealed that PVT-1 expression level was an independent risk factor for overall survival of colorectal cancer patients.Conclusion:PVT-1, which maps to 8q24, generates antiapoptotic activity in CRC, and abnormal expression of PVT-1 was a prognostic indicator for CRC patients.British Journal of Cancer advance online publication 5 November 2013; doi:10.1038/bjc.2013.698 [www.bjcancer.com](http://www.bjcancer.com).

[458]

**TÍTULO / TITLE:** - Differential susceptibility to hydrogen sulfide-induced apoptosis between PHLDA1-overexpressing oral cancer cell lines and oral keratinocytes: Role of PHLDA1 as an apoptosis suppressor.

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

**REVISTA / JOURNAL:** - Exp Cell Res. 2013 Nov 20. pii: S0014-4827(13)00475-8. doi: 10.1016/j.yexcr.2013.10.023.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.yexcr.2013.10.023](#)

**AUTORES / AUTHORS:** - Murata T; Sato T; Kamoda T; Moriyama H; Kumazawa Y; Hanada N

**INSTITUCIÓN / INSTITUTION:** - Department of Translational Research, Tsurumi University School of Dental Medicine, Yokohama 230-8501, Japan; Department of Oral Health, School of Life Dentistry, Nippon Dental University, Tokyo 102-0071, Japan. Electronic address: [murata-ta@tsurumi-u.ac.jp](mailto:murata-ta@tsurumi-u.ac.jp).

**RESUMEN / SUMMARY:** - Hydrogen sulfide (H<sub>2</sub>S) is a novel gasotransmitter that plays multiple biological roles in various body systems. In addition to its endogenous production, H<sub>2</sub>S is produced by bacteria colonizing digestive organs, including the oral cavity. H<sub>2</sub>S was previously shown to enhance pro-apoptotic effects in cancer cell lines, although the mechanisms involved remain unclear. To properly assess the anti-cancer effects of H<sub>2</sub>S, however, investigations of apoptotic effects in normal cells are also

necessary. The aims of this study were (1) to compare the susceptibility to H<sub>2</sub>S-induced apoptosis between the oral cancer cell line Ca9-22 and oral keratinocytes that were derived from healthy gingiva, and (2) to identify candidate genes involved in the induction of apoptosis by H<sub>2</sub>S. The susceptibility to H<sub>2</sub>S-induced apoptosis in Ca9-22 cells was significantly higher than that in keratinocytes. H<sub>2</sub>S exposure in Ca9-22 cells, but not keratinocytes, enhanced the expression of pleckstrin homology-like domain, family A, member 1 (PHLDA1), which was identified through a differential display method. In addition, PHLDA1 expression increased during actinomycin D-induced apoptosis in Ca9-22 cells. Knockdown of PHLDA1 expression by small interfering RNA in Ca9-22 cells led to expression of active caspase 3, thus indicating apoptosis induction. The tongue cancer cell line SCC-25, which expresses PHLDA1 at a high level, showed similar effects. Our data indicate that H<sub>2</sub>S is an anti-cancer compound that may contribute to the low incidence of oral cancer. Furthermore, we demonstrated the role of PHLDA1 as an apoptosis suppressor.

[459]

**TÍTULO / TITLE:** - DMS triggers apoptosis associated with the inhibition of SPHK1/NF-kappaB activation and increase in intracellular Ca<sup>2+</sup> concentration in human cancer cells.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2014 Jan;33(1):17-24. doi: 10.3892/ijmm.2013.1541. Epub 2013 Oct 30.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1541](#)

**AUTORES / AUTHORS:** - Chen K; Pan Q; Gao Y; Yang X; Wang S; Peppelenbosch MP; Kong X

**INSTITUCIÓN / INSTITUTION:** - Bio-X Center, College of Life Sciences, Zhejiang Sci-Tech University, Hangzhou, Zhejiang 310018, P.R. China.

**RESUMEN / SUMMARY:** - N,N-Dimethyl-D-erythro-sphingosine (DMS) is known to induce cell apoptosis by specifically inhibiting sphingosine kinase 1 (SPHK1) and modulating the activity of cellular ceramide levels. The present study investigated the effects and the mechanism(s) of action of DMS in human lung cancer cells. We found that DMS dose-dependently suppressed cell proliferation and induced cell apoptosis in the human lung cancer cell line, A549. Mechanistically, treatment with DMS suppressed the activation of SPHK1 and nuclear factor-kappaB (NF-kappaB) p65, but increased intracellular [Ca<sup>2+</sup>]<sub>i</sub> in A549 cells. This study demonstrates that DMS triggers the apoptosis of human lung cancer cells through the modulation of SPHK1, NF-kappaB and calcium signaling. These molecules may represent targets for anticancer drug design.

[460]

**TÍTULO / TITLE:** - Mycophenolic acid attenuates the tumour necrosis factor-alpha-mediated proinflammatory response in endothelial cells by blocking the MAPK/NF-kappaB and ROS pathways.

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

**REVISTA / JOURNAL:** - Eur J Clin Invest. 2013 Oct 17. doi: 10.1111/eci.12191.

●● Enlace al texto completo (gratis o de pago) [1111/eci.12191](#)

**AUTORES / AUTHORS:** - Olejarz W; Bryk D; Zapolska-Downar D; Malecki M; Stachurska A; Sitkiewicz D

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Clinical Chemistry, The Warsaw Medical University, Warsaw, Poland.

**RESUMEN / SUMMARY:** - BACKGROUND: Mycophenolate mofetil (MMF) has beneficial effects in cardiac transplant patients beyond the suppression of tissue rejection. Moreover, mycophenolic acid (MPA), its active metabolite, has been associated with positive effects on atherosclerosis in animal models. The attachment of leukocytes to the vascular endothelium and the subsequent migration of these cells into the vessel wall are early events in inflammation and atherosclerosis. The aim of this study was to investigate the effects of MPA on tumour necrosis-alpha (TNF-alpha)-induced, endothelial cell proinflammatory responses and the underlying mechanisms. METHODS AND RESULTS: Human aortic endothelial cells (HAECs) were treated with different concentrations (primarily 50 µM) of MPA before treatment with TNF-alpha. The surface protein and mRNA expressions of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were determined by flow cytometry and real-time RT-PCR, respectively. Adhesion of leukocytes to TNF-alpha-treated HAECs was evaluated by an adhesion assay. Activation of mitogen-activated protein kinase (MAPK) and nuclear factor-kappaB (NF-kappaB) was evaluated by measuring the levels of their phosphorylation using flow cytometry. NF-kappaB p65 translocation was detected by Western blotting. The production of reactive oxygen species (ROS) was determined by reduction in fluorescent 2',7'-dichlorofluorescein diacetate (H2 DCFH-DA). MPA significantly inhibits TNF-alpha-induced ICAM-1, VCAM-1 surface protein and mRNA expression as well as adhesion of mononuclear leukocytes to HAEC. ICAM-1 and VCAM-1 expressions were also reduced by antioxidants such as pyrrolidine dithiocarbamate, diphenylene iodonium and apocynin. MPA inhibited TNF-alpha-stimulated ROS generation similarly to apocynin. TNF-alpha increased ICAM-1 and VCAM-1 expression via c-Jun NH2-terminal kinase (JNK), extracellular signal-regulated kinase (ERK1/2) and p38 MAPK. MPA and apocynin inhibited TNF-alpha-induced phosphorylation of all three MAP kinases. Furthermore, TNF-alpha-induced NF-kappaB activation was attenuated by SP600125 (JNK inhibitor), PD98059 (ERK1/2 inhibitor), SB203580 (p38 MAPK inhibitor) and MPA. MPA also inhibited TNF-alpha-induced nuclear translocation of NF-kappaB p65. CONCLUSION: These results suggest that, in addition to the prevention of rejection, MPA may be a promising approach for the treatment of inflammatory vascular disease.

[461]

**TÍTULO / TITLE:** - Synthetic polysulfane derivatives induce cell cycle arrest and apoptotic cell death in human hematopoietic cancer cells.

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

**REVISTA / JOURNAL:** - Food Chem Toxicol. 2013 Oct 21. pii: S0278-6915(13)00695-9. doi: 10.1016/j.fct.2013.10.020.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.fct.2013.10.020](#)

**AUTORES / AUTHORS:** - Czepukojc B; Baltés AK; Cerella C; Kelkel M; Viswanathan UM; Salm F; Burkholz T; Schneider C; Dicato M; Montenarh M; Jacob C; Diederich M

**INSTITUCIÓN / INSTITUTION:** - Division of Bioorganic Chemistry, School of Pharmacy, Saarland University, Campus B 2.1, D-66123 Saarbruecken, Germany; Medizinische Biochemie und Molekularbiologie, Universitat des Saarlandes, Gebaude 44, D-66424 Homburg, Germany.

**RESUMEN / SUMMARY:** - Natural polysulfanes including diallyltrisulfide (DATS) and diallyltetrasulfide (DATTS) from garlic possess antimicrobial, chemopreventive and anticancer properties. However these compounds exhibit chemical instability and reduced solubility, which prevents their potential clinical applicability. We synthesized six DATS and DATTS derivatives, based on the polysulfane motif, expected to exhibit improved physical and chemical properties and verified their biological activity on human leukemia cells. We identified four novel cytotoxic compounds (IC50 values: compound 1, 24.96±12.37µM; compound 2, 22.82±4.20µM; compound 3, 3.86±1.64µM and compound 5, 40.62±10.07µM, compared to DATTS: IC50: 9.33±3.86µM). These polysulfanes possess excellent differential toxicity, as they did not affect proliferating mononuclear blood cells from healthy donors. We further demonstrated ability of active compounds to induce apoptosis in leukemia cells by analysis of nuclear fragmentation and of cleavage of effector and executioner caspases. Apoptosis was preceded by accumulation of cells in G2/M phase with a pro-metaphase-like nuclear pattern as well as microtubular alterations. Prolonged and persistent arrest of cancer cells in early mitosis by the benzyl derivative identifies this compound as the most stable and effective one for further mechanistic and in vivo studies.

[462]

**TÍTULO / TITLE:** - Role of long non-coding RNA HULC in cell proliferation, apoptosis and tumor metastasis of gastric cancer: A clinical and in vitro investigation.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):358-64. doi: 10.3892/or.2013.2850. Epub 2013 Nov 14.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2850](#)

**AUTORES / AUTHORS:** - Zhao Y; Guo Q; Chen J; Hu J; Wang S; Sun Y

**INSTITUCIÓN / INSTITUTION:** - Department of Minimally Invasive Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, P.R. China.

**RESUMEN / SUMMARY:** - Long non-coding RNAs (lncRNAs) are emerging as key molecules in human cancer. Highly upregulated in liver cancer (HULC), an lncRNA, has recently been revealed to be involved in hepatocellular carcinoma development and progression. It remains unclear, however, whether HULC plays an oncogenic role in human gastric cancer (GC). In the present study, we demonstrated that HULC was significantly overexpressed in GC cell lines and GC tissues compared with normal controls, and this overexpression was correlated with lymph node metastasis, distant metastasis and advanced tumor node metastasis stages. In addition, a receiver operating characteristic (ROC) curve was constructed to evaluate the diagnostic values and the area under the ROC curve of HULC was up to 0.769. To uncover its functional importance, gain- and loss-of-function studies were performed to evaluate the effect of HULC on cell proliferation, apoptosis and invasion in vitro. Overexpression of HULC promoted proliferation and invasion and inhibited cell apoptosis in SGC7901 cells, while knockdown of HULC in SGC7901 cells showed the opposite effect.

Mechanistically, we discovered that overexpression of HULC could induce patterns of autophagy in SGC7901 cells; more importantly, autophagy inhibition increased overexpression of HULC cell apoptosis. We also determined that silencing of HULC effectively reversed the epithelial-to-mesenchymal transition (EMT) phenotype. In summary, our results suggest that HULC may play an important role in the growth and tumorigenesis of human GC, which provides us with a new biomarker in GC and perhaps a potential target for GC prevention, diagnosis and therapeutic treatment.

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[463]

**TÍTULO / TITLE:** - A low molecular weight zinc-dipicolylamine-based probe detects apoptosis during tumour treatment better than an annexin V-based probe.

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

**REVISTA / JOURNAL:** - Eur Radiol. 2013 Oct 11.

●● Enlace al texto completo (gratis o de pago) [1007/s00330-013-3014-8](#)

**AUTORES / AUTHORS:** - Palmowski K; Rix A; Lederle W; Behrendt FF; Mottaghy FM; Gray BD; Pak KY; Palmowski M; Kiessling F

**INSTITUCIÓN / INSTITUTION:** - Department of Experimental Molecular Imaging, RWTH-Aachen University, Pauwelsstrasse 30, 52074, Aachen, Germany.

**RESUMEN / SUMMARY:** - OBJECTIVES: Molecular imaging of apoptosis is frequently discussed for monitoring cancer therapies. Here, we compare the low molecular weight phosphatidylserine-targeting ligand zinc<sup>2+</sup>-dipicolylamine (Zn<sup>2+</sup>-DPA) with the established but reasonably larger protein annexin V. METHODS: Molecular apoptosis imaging with the fluorescently labelled probes annexin V (750 nm, 36 kDa) and Zn<sup>2+</sup>-DPA (794 nm, 1.84 kDa) was performed in tumour-bearing mice (A431). Three animal groups were investigated: untreated controls and treated tumours after 1 or 4 days of anti-angiogenic therapy (SU11248). Additionally, muPET with 18 F-FDG was performed. Imaging data were displayed as tumour-to-muscle ratio (TMR) and validated by quantitative immunohistochemistry. RESULTS: Compared with untreated control tumours, TUNEL staining indicated significant apoptosis after 1 day (P < 0.05) and 4 days (P < 0.01) of treatment. Concordantly, Zn<sup>2+</sup>-DPA uptake increased significantly after 1 day (P < 0.05) and 4 days (P < 0.01). Surprisingly, annexin V failed to detect significant differences between control and treated animals. Contrary to the increasing uptake of Zn<sup>2+</sup>-DPA, 18 F-FDG tumour uptake decreased significantly at days 1 (P < 0.05) and 4 (P < 0.01). CONCLUSIONS: Increase in apoptosis during anti-angiogenic therapy was detected significantly better with the low molecular weight probe Zn<sup>2+</sup>-DPA than with the annexin V-based probe. Additionally, significant treatment effects were detectable as early using Zn<sup>2+</sup>-DPA as with measurements of the glucose metabolism using 18 F-FDG. KEY POINTS: \* The detection of apoptosis by non-invasive imaging is important in oncology. \* A new low molecular weight probe Zn<sup>2+</sup>-DPA shows promise in depicting anti-angiogenic effects. \* The small Zn<sup>2+</sup>-DPA ligand appears well suited for monitoring therapy. \* Treatment effects are detectable just as early with Zn<sup>2+</sup>-DPA as with 18 F-FDG.

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[464]

**TÍTULO / TITLE:** - A Multifactorial Histopathologic Score for the Prediction of Prognosis of Resected Esophageal Adenocarcinomas After Neoadjuvant Chemotherapy.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Nov 27.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3410-y](#)

**AUTORES / AUTHORS:** - Langer R; Becker K; Zlobec I; Gertler R; Sisic L; Buchler M; Lordick F; Slotta-Huspenina J; Weichert W; Hofler H; Feith M; Ott K

**INSTITUCIÓN / INSTITUTION:** - Institute of Pathology, University of Bern, Bern, Switzerland, [rupert.langer@pathology.unibe.ch](mailto:rupert.langer@pathology.unibe.ch).

**RESUMEN / SUMMARY:** - BACKGROUND: For esophageal adenocarcinoma treated with neoadjuvant chemotherapy, postoperative staging classifications initially developed for non-pretreated tumors may not accurately predict prognosis. We tested whether a multifactorial TNM-based histopathologic prognostic score (PRSC), which additionally applies to tumor regression, may improve estimation of prognosis compared with the current Union for International Cancer Control/American Joint Committee on Cancer (UICC) staging system. PATIENTS AND METHODS: We evaluated esophageal adenocarcinoma specimens following cis/oxaliplatin-based therapy from two separate centers (center 1: n = 280; and center 2: n = 80). For the PRSC, each factor was assigned a value from 1 to 2 (ypT0-2 = 1 point; ypT3-4 = 2 points; ypN0 = 1 point; ypN1-3 = 2 points;  $\leq 50\%$  residual tumor/tumor bed = 1 point;  $> 50\%$  residual tumor/tumor bed = 2 points). The three-tiered PRSC was based on the sum value of these factors (group A: 3; group B: 4-5; group C: 6) and was correlated with patients' overall survival (OS). RESULTS: The PRSC groups showed significant differences with respect to OS (p < 0.0001; hazard ratio [HR] 2.2 [95 % CI 1.7-2.8]), which could also be demonstrated in both cohorts separately (center 1 p < 0.0001; HR 2.48 [95 % CI 1.8-3.3] and center 2 p = 0.015; HR 1.7 [95 % CI 1.1-2.6]). Moreover, the PRSC showed a more accurate prognostic discrimination than the current UICC staging system (p < 0.0001; HR 1.15 [95 % CI 1.1-1.2]), and assessment of two goodness-of-fit criteria (Akaike Information Criterion and Schwarz Bayesian Information Criterion) clearly supported the superiority of PRSC over the UICC staging. CONCLUSION: The proposed PRSC clearly identifies three subgroups with different outcomes and may be more helpful for guiding further therapeutic decisions than the UICC staging system.

[465]

**TÍTULO / TITLE:** - Osthole inhibits proliferation and induces apoptosis in human osteosarcoma cells.

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

**REVISTA / JOURNAL:** - Int J Clin Pharmacol Ther. 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [5414/CP201923](#)

**AUTORES / AUTHORS:** - Ding Y; Lu X; Hu X; Ma J; Ding H

**RESUMEN / SUMMARY:** - Objective: The purpose of this study was to investigate the effect of osthole on osteosarcoma cell proliferation and apoptosis. Method: Cell counting Kit-8 assay was performed to establish the effects of osthole on osteosarcoma MG-63 cell proliferation. Annexin V-FITC/PI was performed to analyze the apoptotic rate of the cells. Result: The inhibitory effects of osthole on the expression of BCL-2, BAX, and caspase-3 were detected by Western blotting. Osthole inhibited the growth of human osteosarcoma MG-63 cells by inhibiting cell proliferation and induced cell apoptosis. Western blotting demonstrated that osthole downregulated

the expressions of BCL-2 and caspase-3 and upregulated the expression of BAX in human osteosarcoma cells. Conclusion: Osthole can inhibit osteosarcoma cell proliferation and induced apoptosis effectively in a dose-dependent manner through downregulating the expression of BCL-2 and caspase-3 proteins levels and upregulating the expression of BAX proteins levels.

[466]

**TÍTULO / TITLE:** - Expression of RRM1 and RRM2 as a novel prognostic marker in advanced non-small cell lung cancer receiving chemotherapy.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1255-4](#)

**AUTORES / AUTHORS:** - Wang L; Meng L; Wang XW; Ma GY; Chen JH

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, 250021, China.

**RESUMEN / SUMMARY:** - The aim of this study was to examine the prognostic value of BRCA1, RRM1, and RRM2 in patients with non-small cell lung cancer (NSCLC) who received adjuvant chemotherapy. A total of 418 patients who underwent curative pulmonary resection were obtained between January 2007 and November 2009. The relative cDNA quantification for BRCA1, RRM1, and RRM2 was conducted using a fluorescence-based, real-time detection method, and beta-actin was used as a reference gene. The low expression of RRM1 and RRM2 significantly increased the platinum-based chemotherapy response (For RRM1: odds ratio (OR) = 2.09, 95 % confidence interval (CI) = 1.38-3.18; For RRM2: OR = 1.64, 95 % CI = 1.09-2.48). The univariate analysis indicated that low expression of RRM1 attained a longer time to progression and overall survival time, with HR (95 % CI) of 0.50 (0.33-0.77) and 0.60 (0.39-0.92), respectively. Similarly, low expression of RRM2 had a longer time to progression and overall survival, with HR (95 % CI) of 0.57 (0.38-0.86) and 0.47 (0.31-0.71), respectively. In conclusion, low expression of RRM1 and RRM2 could be used to predict the treatment response to platinum-based chemotherapy and survival in NSCLC. The RRM1 and RRM2 could substantially contribute to the future design of individualized cancer treatment in NSCLC patients.

[467]

**TÍTULO / TITLE:** - Antiproliferative, antiandrogenic and cytotoxic effects of novel caffeic acid derivatives in LNCaP human androgen-dependent prostate cancer cells.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem. 2013 Nov 15;21(22):7182-93. doi: 10.1016/j.bmc.2013.08.057. Epub 2013 Sep 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmc.2013.08.057](#)

**AUTORES / AUTHORS:** - Sanderson JT; Clabault H; Patton C; Lassalle-Claux G; Jean-Francois J; Pare AF; Hebert MJ; Surette ME; Touaibia M

**INSTITUCIÓN / INSTITUTION:** - INRS-Institut Armand-Frappier, 531, boulevard des Prairies, Laval, QC H7V 1B7, Canada. Electronic address: [thomas.sanderson@iaf.inrs.ca](mailto:thomas.sanderson@iaf.inrs.ca).

**RESUMEN / SUMMARY:** - Caffeic acid and its naturally occurring derivative caffeic acid phenethyl ester (CAPE) have antiproliferative and cytotoxic properties in a variety of cancer cell lines without displaying significant toxicity toward healthy cells, and are considered to be potential anticancer agents. However, little is known about their effects on prostate cancer cells. We synthesized and evaluated the effects of caffeic acid, CAPE (2) and 18 synthetic derivatives on cell viability and androgen-dependent cell proliferation, subcellular localisation and expression of androgen receptor (AR) and secretion of prostate-specific antigen (PSA) in LNCaP human hormone-dependent prostate cancer cells. Several synthetic derivatives of CAPE were strong, concentration-dependent cytotoxic agents in LNCaP cells with IC50 values in the 6.8-26.6  $\mu\text{M}$  range, potencies that were up to five-fold greater than that of CAPE (33.7 $\pm$ 4.0  $\mu\text{M}$ ). A number of caffeic acid derivatives were inhibitors of androgen-stimulated LNCaP cell proliferation with concomitant inhibition of DHT-stimulated PSA secretion. Compound 24 was the most cytotoxic and antiproliferative caffeic acid derivative (IC50 values of 6.8 $\pm$ 0.3 and 2.4 $\pm$ 0.8  $\mu\text{M}$ , respectively) inhibiting DHT-stimulated cell proliferation and PSA secretion statistically significantly at concentrations as low as 0.3  $\mu\text{M}$ . Exposure to DHT increased cytoplasmic and nuclear AR levels and co-treatment with increasing concentrations of compound 24 or CAPE (2), notably, further increased these levels. In conclusion, a number of synthetic derivatives of caffeic acid are potent inhibitors of androgen-dependent prostate cancer cell proliferation and viability, acting, at least in part, via an antiandrogenic mechanism that involves increased nuclear accumulation of (presumably inactive) AR.

[468]

**TÍTULO / TITLE:** - Effect of hyperbaric oxygenation and gemcitabine on apoptosis of pancreatic ductal tumor cells in vitro.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):4827-32.

**AUTORES / AUTHORS:** - Bosco G; Guizzon L; Yang Z; Camporesi E; Casarotto A; Bosio C; Mangar D; Chen C; Cannato M; Toniolo L; Garetto G; Nasole E; Bassi C

**INSTITUCIÓN / INSTITUTION:** - Department of Anesthesiology, SUNY Upstate Medical University, Syracuse, NY, 13210, U.S.A. [yangz@upstate.edu](mailto:yangz@upstate.edu).

**RESUMEN / SUMMARY:** - BACKGROUND: Gemcitabine is first-line therapy for advanced pancreatic ductal adenocarcinoma (PDAC) with a poor survival and response rate. Hyperbaric oxygenation (HBO) enhances delivery of oxygen to hypoxic tumor cells and increases their susceptibility to cytotoxic effects of chemotherapy. We hypothesized that the anticancer activity of gemcitabine (GEM) may be enhanced if tumor cells are placed in an oxygen-rich environment. The present study evaluated the effects of gemcitabine, HBO and their combination on apoptosis of tumor cells. MATERIALS AND METHODS: PANC-1 and AsPc-1 PDAC tumor cell lines were used. Cultured tumor cells were treated with GEM at its growth-inhibitory concentration (IC50) and HBO at 2.5 ATA for 90 min or a combination of both (HBO then GEM and GEM then HBO). Twenty-four hours later, apoptotic cells in each group were analyzed and the apoptotic index (AI) was calculated. RESULTS: PANC-1 cell line: HBO alone had no effect on AI: 6.5 $\pm$ 0.1 vs. 5.9 $\pm$ 0.1. HBO before and after gemcitabine did not further increase AI: 8.2 $\pm$ 0.1 (HBO-GEM), 8.5 $\pm$ 0.1 (GEM-HBO) vs. 8.1 $\pm$ 0.1 (GEM). The combination of HBO and gemcitabine significantly increased AI: 10.7 $\pm$ 0.02

( $p < 0.001$  vs. all groups). AsPc-1 cell line: HBO-alone had no effect on AI:  $5.9 \pm 0.1$  vs.  $5.9 \pm 0.1$ . HBO before and after gemcitabine did not further increase AI:  $8.2 \pm 0.1$  (HBO-GEM),  $8.4 \pm 0.1$  (GEM-HBO) vs.  $8.0 \pm 0.1$  (GEM). The combination of HBO and gemcitabine significantly increased AI:  $9.7 \pm 0.1$  ( $p < 0.001$  vs. all groups).  
CONCLUSION: HBO-alone, whether administered before and after gemcitabine has no effect on apoptosis of PDAC cells in vitro. HBO significantly enhanced gemcitabine-induced apoptosis when administered during gemcitabine. Our findings suggest that the time window would be critical for using HBO as adjuvant to chemotherapy.

[469]

**TÍTULO / TITLE:** - Targeting elongation factor-2 kinase (eEF-2K) induces apoptosis in human pancreatic cancer cells.

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

**REVISTA / JOURNAL:** - Apoptosis. 2013 Nov 6.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10495-013-0927-2](#)

**AUTORES / AUTHORS:** - Ashour AA; Abdel-Aziz AA; Mansour AM; Alpay SN; Huo L; Ozpolat B

**INSTITUCIÓN / INSTITUTION:** - Department of Experimental Therapeutics, Unit 422, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX, 77030, USA.

**RESUMEN / SUMMARY:** - Pancreatic cancer (PaCa) is one of the most aggressive, apoptosis-resistant and currently incurable cancers with a poor survival rate. Eukaryotic elongation factor-2 kinase (eEF-2K) is an atypical kinase, whose role in PaCa survival is not yet known. Here, we show that eEF-2K is overexpressed in PaCa cells and its down-regulation induces apoptotic cell death. Rottlerin (ROT), a polyphenolic compound initially identified as a PKC-delta inhibitor, induces apoptosis and autophagy in a variety of cancer cells including PaCa cells. We demonstrated that ROT induces intrinsic apoptosis, with dissipation of mitochondrial membrane potential ( $\Delta\psi$ ), and stimulates extrinsic apoptosis with concomitant induction of TNF-related apoptosis inducing ligand (TRAIL) receptors, DR4 and DR5, with caspase-8 activation, in PANC-1 and MIAPaCa-2 cells. Notably, while none of these effects were dependent on PKC-delta inhibition, ROT down-regulates eEF-2K at mRNA level, and induce eEF-2K protein degradation through ubiquitin-proteasome pathway. Down-regulation of eEF-2K recapitulates the events observed after ROT treatment, while its over-expression suppressed the ROT-induced apoptosis. Furthermore, eEF-2K regulates the expression of tissue transglutaminase (TG2), an enzyme previously implicated in proliferation, drug resistance and survival of cancer cells. Inhibition of eEF-2K/TG2 axis leads to caspase-independent apoptosis which is associated with induction of apoptosis-inducing factor (AIF). Collectively, these results indicate, for the first time, that the down-regulation of eEF-2K leads to induction of intrinsic, extrinsic as well as AIF-dependent apoptosis in PaCa cells, suggesting that eEF-2K may represent an attractive therapeutic target for the future anticancer agents in PaCa.

[470]

**TÍTULO / TITLE:** - Autotaxin-lysophosphatidic Acid signaling axis mediates tumorigenesis and development of acquired resistance to sunitinib in renal cell carcinoma.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Dec 1;19(23):6461-72. doi: 10.1158/1078-0432.CCR-13-1284. Epub 2013 Oct 11.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1284](#)

**AUTORES / AUTHORS:** - Su SC; Hu X; Kenney PA; Merrill MM; Babaian KN; Zhang XY; Maity T; Yang SF; Lin X; Wood CG

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of Urology and Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan.

**RESUMEN / SUMMARY:** - PURPOSE: Sunitinib is currently considered as the standard treatment for advanced renal cell carcinoma (RCC). We aimed to better understand the mechanisms of sunitinib action in kidney cancer treatment and in the development of acquired resistance. EXPERIMENTAL DESIGN: Gene expression profiles of RCC tumor endothelium in sunitinib-treated and -untreated patients were analyzed and verified by quantitative PCR and immunohistochemistry. The functional role of the target gene identified was investigated in RCC cell lines and primary cultures in vitro and in preclinical animal models in vivo. RESULTS: Altered expression of autotaxin, an extracellular lysophospholipase D, was detected in sunitinib-treated tumor vasculature of human RCC and in the tumor endothelial cells of RCC xenograft models when adapting to sunitinib. ATX and its catalytic product, lysophosphatidic acid (LPA), regulated the signaling pathways and cell motility of RCC in vitro. However, no marked in vitro effect of ATX-LPA signaling on endothelial cells was observed. Functional blockage of LPA receptor 1 (LPA1) using an LPA1 antagonist, Ki16425, or gene silencing of LPA1 in RCC cells attenuated LPA-mediated intracellular signaling and invasion responses in vitro. Ki16425 treatment also dampened RCC tumorigenesis in vivo. In addition, coadministration of Ki16425 with sunitinib prolonged the sensitivity of RCC to sunitinib in xenograft models, suggesting that ATX-LPA signaling in part mediates the acquired resistance against sunitinib in RCC. CONCLUSIONS: Our results reveal that endothelial ATX acts through LPA signaling to promote renal tumorigenesis and is functionally involved in the acquired resistance of RCC to sunitinib. Clin Cancer Res; 19(23); 6461-72. ©2013 AACR.

[471]

**TÍTULO / TITLE:** - Prostate cancer gene 3 and multiparametric magnetic resonance can reduce unnecessary biopsies: decision curve analysis to evaluate predictive models.

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

**REVISTA / JOURNAL:** - Urology. 2013 Dec;82(6):1355-62. doi: 10.1016/j.urology.2013.06.078. Epub 2013 Sep 29.

●● Enlace al texto completo (gratis o de pago) [1016/j.urology.2013.06.078](#)

**AUTORES / AUTHORS:** - Busetto GM; De Berardinis E; Sciarra A; Panebianco V; Giovannone R; Rosato S; D'Errigo P; Di Silverio F; Gentile V; Salciccia S

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Sapienza University of Rome, Rome, Italy.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To overcome the well-known prostate-specific antigen limits, several new biomarkers have been proposed. Since its introduction in clinical practice, the urinary prostate cancer gene 3 (PCA3) assay has shown promising results for prostate cancer (PC) detection. Furthermore, multiparametric magnetic resonance imaging (mMRI) has the ability to better describe several aspects of PC. **METHODS:** A prospective study of 171 patients with negative prostate biopsy findings and a persistent high prostate-specific antigen level was conducted to assess the role of mMRI and PCA3 in identifying PC. All patients underwent the PCA3 test and mMRI before a second transrectal ultrasound-guided prostate biopsy. The accuracy and reliability of PCA3 (3 different cutoff points) and mMRI were evaluated. Four multivariate logistic regression models were analyzed, in terms of discrimination and the cost benefit, to assess the clinical role of PCA3 and mMRI in predicting the biopsy outcome. A decision curve analysis was also plotted. **RESULTS:** Repeated transrectal ultrasound-guided biopsy identified 68 new cases (41.7%) of PC. The sensitivity and specificity of the PCA3 test and mMRI was 68% and 49% and 74% and 90%, respectively. Evaluating the regression models, the best discrimination (area under the curve 0.808) was obtained using the full model (base clinical model plus mMRI and PCA3). The decision curve analysis, to evaluate the cost/benefit ratio, showed good performance in predicting PC with the model that included mMRI and PCA3. **CONCLUSION:** mMRI increased the accuracy and sensitivity of the PCA3 test, and the use of the full model significantly improved the cost/benefit ratio, avoiding unnecessary biopsies.

[472]

**TÍTULO / TITLE:** - NSC126188 induces apoptosis of prostate cancer PC-3 cells through inhibition of Akt membrane translocation, FoxO3a activation, and RhoB transcription.

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

**REVISTA / JOURNAL:** - Apoptosis. 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0905-8](#)

**AUTORES / AUTHORS:** - Won KJ; Kim BK; Han G; Lee K; Jung YJ; Kim HM; Song KB; Chung KS; Won M

**INSTITUCIÓN / INSTITUTION:** - Medical Genome Research Center, KRIBB, Taejeon, 305-806, Korea.

**RESUMEN / SUMMARY:** - We previously reported that NSC126188 caused apoptosis of cancer cells by inducing expression of RhoB. We here present that NSC126188 induces apoptosis of prostate cancer PC-3 cells by inhibiting Akt/FoxO3 signaling, which mediates RhoB upregulation. The apoptosis and Akt dephosphorylation caused by NSC126188 was not substantially relieved by overexpressing wild-type Akt but was relieved by overexpressing constitutively active Akt (CA-Akt) or myristoylated Akt (myr-Akt). Furthermore, overexpression of CA-Akt or myr-Akt downregulated RhoB expression, indicating that RhoB expression is regulated by Akt signaling. Interestingly, membrane translocation of GFP-Akt by insulin exposure was abolished in the cells pretreated with NSC126188 suggesting that NSC126188 directly interfered with translocation of Akt to the plasma membrane. In addition, NSC126188 activated FoxO3a by dephosphorylating S253 via Akt inhibition. Activated FoxO3a translocated

to the nucleus and increased transcription of RhoB and other target genes. PC-3 cells transiently overexpressing FoxO3a exhibited increased RhoB expression and apoptosis in response to NSC126188. Conversely, FoxO3a knockdown reduced NSC126188-induced RhoB expression and cell death. These results suggest that RhoB may be a target gene of FoxO3a and is regulated by Akt signaling. Taken together, NSC126188 induces apoptosis of PC-3 cells by interfering with membrane recruitment of Akt, resulting in Akt dephosphorylation and FoxO3a activation, which leads to transcription of RhoB.

[473]

**TÍTULO / TITLE:** - Sodium taurocholate cotransporting polypeptide mediates dual actions of deoxycholic acid in human hepatocellular carcinoma cells: enhanced apoptosis versus growth stimulation.

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

**REVISTA / JOURNAL:** - J Cancer Res Clin Oncol. 2013 Nov 27.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1554-6](#)

**AUTORES / AUTHORS:** - Jang ES; Yoon JH; Lee SH; Lee SM; Lee JH; Yu SJ; Kim YJ; Lee HS; Kim CY

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul National University Hospital, 101 Daehakro, Chongno-gu, Seoul, 110-744, Republic of Korea.

**RESUMEN / SUMMARY:** - PURPOSE: The hydrophobic bile acid, deoxycholic acid (DC), can induce apoptosis in hepatocytes. The roles of DC and its transporter are not yet established in hepatocellular carcinoma (HCC) cells. We investigated DC-induced alterations in HCC cell growth, with a particular focus on the effect of the expression of bile acid (BA)-transporting Na<sup>+</sup>-dependent taurocholic cotransporting polypeptides (NTCPs). METHODS: We determined NTCP expression in four human HCC cell lines: Huh-BAT, Huh-7, SNU-761, and SNU-475. NTCP expression and apoptotic signaling cascades were examined by immunoblot analyses. Cell viability was assessed using the 3,4-(5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium salt assay. Wound healing and invasion assays were performed to evaluate cell migration and invasion abilities. Real-time polymerase chain reaction was performed to measure IL-8 expression levels. Nuclear factor kappa B (NF-kappaB) activity was evaluated by enzyme-linked immunosorbent assay. RESULTS: The HCC cell lines revealed varying NTCP expression levels, and DC treatment had dual effects, depending on NTCP expression. DC induced apoptosis in NTCP-positive HCC cells, especially under hypoxic conditions. In NTCP-negative HCC cells, simultaneous treatment with DC and cyclooxygenase inhibitor markedly decreased aggressive cellular behaviors via the inhibition of NF-kappaB/COX-2/IL-8 pathways. CONCLUSION: Hydrophobic bile acid offers therapeutic potential for patients with advanced HCC via different mechanisms depending on NTCP expression levels within the tumor.

[474]

**TÍTULO / TITLE:** - Combination of liquiritin, isoliquiritin and isoliquirigenin induce apoptotic cell death through upregulating p53 and p21 in the A549 non-small cell lung cancer cells.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):298-304. doi: 10.3892/or.2013.2849. Epub 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2849](#)

**AUTORES / AUTHORS:** - Zhou Y; Ho WS

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong, SAR, P.R. China.

**RESUMEN / SUMMARY:** - Liquiritin, isoliquiritin and isoliquirigenin are the active polyphenols present in Glycyrrhiza uralensis which has been used for the treatment of cancer and its complications. The present study was conducted to evaluate the cytotoxicity and antitumor activity of liquiritin, isoliquiritin and isoliquirigenin on human non-small lung cancer cells including apoptosis-induction, inhibition of apoptotic pathways and to explore the underlying mechanism. Lactate dehydrogenase assays, FITC Annexin V staining assay were performed to evaluate cellular cytotoxicity and apoptosis activity. The results showed that pretreatment with these polyphenols induced apoptosis in A549 cells. Liquiritin, isoliquiritin and isoliquirigenin significantly increased cytotoxicity of, and upregulated p53 and p21 and downregulated the apoptotic pathways. Furthermore, it inhibited cell cycle at the G2/M phase. Western blot analysis showed it significantly decreased the protein expression of PCNA, MDM2, p-GSK-3beta, p-Akt, p-c-Raf, p-PTEN, caspase-3, pro-caspase-8, pro-caspase-9 and PARP, Bcl-2 in a concentration-dependent manner while the protein expression of p53, p21 and Bax was increased. In addition, Akt pathway was downregulated. These findings suggest that liquiritin, isoliquiritin and isoliquirigenin inhibited the p53-dependent pathway and showed crosstalk between Akt activities. These active polyphenols can be an alternative agent for the treatment of lung cancer.

[475]

**TÍTULO / TITLE:** - Induction of G2/M phase cell cycle arrest and apoptosis by ginsenoside Rf in human osteosarcoma MG63 cells through the mitochondrial pathway.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):305-13. doi: 10.3892/or.2013.2815. Epub 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2815](#)

**AUTORES / AUTHORS:** - Shangguan WJ; Li H; Zhang YH

**INSTITUCIÓN / INSTITUTION:** - Department of Traditional Chinese Medicine, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200127, P.R. China.

**RESUMEN / SUMMARY:** - Ginsenosides, extracted from the traditional Chinese herb ginseng, are a series of novel natural anticancer products known for their favorable safety and efficacy profiles. The present study aimed to investigate the cytotoxicity of ginsenoside Rf to human osteosarcoma cells and to explore the anticancer molecular mechanisms of ginsenoside Rf. Five human osteosarcoma cell lines (MG-63, OS732, U-2OS, HOS and SAOS-2) were employed to investigate the cytotoxicity of

ginsenoside Rf by MTT and colony forming assays. After treatment with ginsenoside Rf, MG-63 cells which were the most sensitive to ginsenoside Rf, were subjected to flow cytometry to detect cell cycle distribution and apoptosis, and nuclear morphological changes were visualized by Hoechst 33258 staining. Caspase-3, -8 and -9 activities were also evaluated. The expression of cell cycle markers including cyclin B1 and Cdk1 was detected by RT-PCR and western blotting. The expression of apoptotic genes Bcl-2 and Bax and the release of cytochrome c were also examined by western blotting. Change in the mitochondrial membrane potential was observed by JC-1 staining in situ. Our results demonstrated that the cytotoxicity of ginsenoside Rf to these human osteosarcoma cell lines was dose-dependent, and the MG-63 cells were the most sensitive to exposure to ginsenoside Rf. Additionally, ginsenoside Rf induced G2/M phase cell cycle arrest and apoptosis in MG-63 cells. Furthermore, we observed upregulation of Bax and downregulation of Bcl-2, Cdk1 and cyclin B1, the activation of caspase-3 and -9 and the release of cytochrome c in MG-63 cells following treatment with ginsenoside Rf. Our findings demonstrated that ginsenoside Rf induces G2/M phase cell cycle arrest and apoptosis in human osteosarcoma MG-63 cells through the mitochondrial pathway, suggesting that ginsenoside Rf, as an effective natural product, may have a therapeutic effect on human osteosarcoma.

[476]

**TÍTULO / TITLE:** - Catechin-7-O-xyloside induces apoptosis via endoplasmic reticulum stress and mitochondrial dysfunction in human non-small cell lung carcinoma H1299 cells.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):314-20. doi: 10.3892/or.2013.2840. Epub 2013 Nov 8.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2840](#)

**AUTORES / AUTHORS:** - Yoon JW; Lee JS; Kim BM; Ahn J; Yang KM

**INSTITUCIÓN / INSTITUTION:** - Department of Food Science and Engineering, Ewha Womans University, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - The medicinal plant *Ulmus davidiana* var. *japonica* has significant potential as a cancer chemoprevention agent. Catechin-7-O-xyloside (C7Ox) was purified from ultrafine *U. davidiana* var. *japonica* ethanol extract. In the present study, we investigated the apoptotic effect of C7Ox in the non-small cell lung cancer (NSCLC) cell line H1299. C7Ox treatment induced cell death and decreased plasma membrane integrity, an event typical of apoptosis. C7Ox-induced apoptosis was associated with the proteolytic activation of caspase-6, cleavage of poly(ADP-ribose) polymerase (PARP) and loss of mitochondrial membrane potential. C7Ox also induced the endoplasmic reticulum (ER) stress-regulated pro-apoptotic transcription factor CHOP. The suppression of CHOP expression significantly decreased C7Ox-induced cell death, LDH leakage and caspase-6 activation. Antitumor effects, evaluated based on protracted tumor regression, were observed when nude-mice bearing H1299 xenografts were treated with C7Ox. C7Ox-induced tumor regression was accompanied by enhanced expression of CHOP mRNA. Our data suggest that C7Ox can trigger mitochondrial-mediated apoptosis, and that ER stress is critical for C7Ox-induced apoptosis in H1299 NSCLC cells.

[477]

**TÍTULO / TITLE:** - The BH3 mimetic S1 induces endoplasmic reticulum stress-associated apoptosis in cisplatin-resistant human ovarian cancer cells although it activates autophagy.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2677-84. doi: 10.3892/or.2013.2771. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2771](#)

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**RESUMEN / SUMMARY:** - SKOV3/DDP human ovarian cancer cells have been shown to be resistant to cisplatin. Although the BH3 mimetic S1 induces cell death in several types of tumor cells, it is unclear whether it induces death in drug-resistant cells. Herein, we found that S1 induced endoplasmic reticulum (ER) stress-associated apoptosis in both SKOV3 and SKOV3/DDP cells. S1 activated autophagy at early time points in SKOV3/DDP cells, and inhibition of autophagy increased ER stress-associated apoptosis. Collectively, our data indicate that autophagy plays a protective role, but it cannot protect against S1-induced cell death in cisplatin-resistant SKOV3/DDP cells.

[478]

**TÍTULO / TITLE:** - Global real-time quantitative reverse transcription-polymerase chain reaction detecting proto-oncogenes associated with 14q32 chromosomal translocation as a valuable marker for predicting survival in multiple myeloma.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Dec;37(12):1648-55. doi: 10.1016/j.leukres.2013.09.026. Epub 2013 Oct 18.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.09.026](#)

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**RESUMEN / SUMMARY:** - CCND1, FGFR3 and c-MAF mRNA expression of tumor samples from 123 multiple myeloma patients were analyzed by global RQ/RT-PCR. CCND1, FGFR3 and c-MAF were positive in 44 (36%), 28 (23%) and 16 (13%) of patients, respectively. In 7 patients, both FGFR3 and c-MAF were positive. The expression of c-MAF was independent unfavorable prognostic factors for overall survival (OS). Autologous stem cell transplantation improved progression-free survival of CCND1-positive patients. Bortezomib, thalidomide or lenalidomide extended OS of FGFR3 and/or c-MAF-positive patients. Thus, CCND1, FGFR3 and c-MAF mRNA expression can predict survival and is useful for planning stratified treatment strategies for myeloma patients.

[479]

**TÍTULO / TITLE:** - Targeted cancer therapy - Are the days of systemic chemotherapy numbered?

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

**REVISTA / JOURNAL:** - Maturitas. 2013 Dec;76(4):308-14. doi: 10.1016/j.maturitas.2013.09.008. Epub 2013 Sep 20.

●● Enlace al texto completo (gratis o de pago) [1016/j.maturitas.2013.09.008](#)

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**RESUMEN / SUMMARY:** - Targeted therapy or molecular targeted therapy has been defined as a type of treatment that blocks the growth of cancer cells by interfering with specific cell molecules required for carcinogenesis and tumor growth, rather than by simply interfering with all rapidly dividing cells as with traditional chemotherapy. There is a growing number of FDA approved monoclonal antibodies and small molecules targeting specific types of cancer suggestive of the growing relevance of this therapeutic approach. Targeted cancer therapies, also referred to as “Personalized Medicine”, are being studied for use alone, in combination with other targeted therapies, and in combination with chemotherapy. The objective of personalized medicine is the identification of patients that would benefit from a specific treatment based on the expression of molecular markers. Examples of this approach include bevacizumab and olaparib, which have been designated as promising targeted therapies for ovarian cancer. Combinations of trastuzumab with pertuzumab, or T-DM1 and mTOR inhibitors added to an aromatase inhibitor are new therapeutic strategies for breast cancer. Although this approach has been seen as a major step in the expansion of personalized medicine, it has substantial limitations including its high cost and the presence of serious adverse effects. The Cancer Genome Atlas is a useful resource to identify novel and more effective targets, which may help to overcome the present limitations. In this review we will discuss the clinical outcome of some of these new therapies with a focus on ovarian and breast cancer. We will also discuss novel concepts in targeted therapy, the target of cancer stem cells.

[480]

**TÍTULO / TITLE:** - Effects and Mechanisms of Anti-CD44 Monoclonal Antibody A3D8 on Proliferation and Apoptosis of Sphere-Forming Cells With Stemness From Human Ovarian Cancer.

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

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 Oct;23(8):1367-75. doi: 10.1097/IGC.0b013e3182a1d023.

●● Enlace al texto completo (gratis o de pago) [1097/IGC.0b013e3182a1d023](#)

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**RESUMEN / SUMMARY:** - OBJECTIVE: CD44 human ovarian cancer stem cells (CSCs) and CSC-like cells have been identified and characterized. Compelling evidence has revealed that CD44 is involved in the occurrence and development of cancers. Our previous study showed that sphere-forming cells (SFCs) from the human ovarian cancer cell line SKOV-3 had CSC capacity. Therefore, in the present study, we aimed to investigate the effects and mechanisms of the anti-CD44 monoclonal antibody A3D8 on the proliferation and apoptosis of SFCs to explore novel strategies for the treatment of ovarian cancer. METHODS: We investigated the effects and mechanisms of A3D8 on the proliferation and apoptosis of SFCs using the MTS assay, cell cycle analysis, an annexin V-fluorescein isothiocyanate/propidium iodide kit, Rh123 apoptosis detection kit, real-time reverse transcription polymerase chain reaction and Western blotting. RESULTS: After CD44 ligation by A3D8, SFC cell proliferation was notably attenuated, cell cycle progression was arrested in the S phase, and apoptosis was significantly increased. The effect of A3D8 was enhanced in a dose- and time-dependent manner, and the effect of apoptosis induction by DDP was enhanced by combination treatment with A3D8. Furthermore, the messenger RNA expression levels of p21 and caspase-3 were up-regulated, whereas those of CDK2, cyclinA, and Bcl-2 were down-regulated. The protein expression levels of caspase-3 were up-regulated, whereas those of CDK2, cyclinA, and Bcl-2 were down-regulated. CONCLUSIONS: Our findings indicate that anti-CD44 monoclonal antibodies may be a potential strategy for the treatment of human ovarian cancer after conventional therapy via inhibition of growth and the promotion of apoptosis in SFCs with stemness.

[481]

**TÍTULO / TITLE:** - Decreased secretion of vascular endothelial growth factor is associated with increased apoptosis in vascular tumor derived endothelial cells.

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

**REVISTA / JOURNAL:** - J Physiol Pharmacol. 2013 Aug;64(4):473-7.

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**RESUMEN / SUMMARY:** - Bleomycin is an antineoplastic drug that has recently been employed to treat haemangiomas, the most common vascular tumors of infancy, with very good results. To better understand the mechanism of bleomycin in accelerating haemangioma regression, we have investigated the effects of the drug on vascular tumor inducing endothelial cells (sEnd.2 cells). Cell growth studies were undertaken using crystal violet staining, while morphological studies were undertaken employing transmission electron microscopy. The cells were analyzed for possible apoptosis employing flow cytometry. The expression of Bcl-2 and p53 were investigated using Western blot analysis. In addition, the production of vascular endothelial growth factor was measured using ELISA. Results showed that bleomycin inhibited the growth of these endothelial cells, even in the presence of vascular endothelial growth factor, a

proangiogenic growth factor. Further, there was increased endothelial cell apoptosis, as evidenced by morphological analysis, increased acridine orange staining of cell nuclei and annexin V staining. Apoptosis was associated with an increase in the expression of p53 and a decrease in the expression of the antiapoptotic protein Bcl-2.

[482]

**TÍTULO / TITLE:** - 18beta-Glycyrrhetic acid induces apoptosis in pituitary adenoma cells via ROS/MAPKs-mediated pathway.

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

**REVISTA / JOURNAL:** - J Neurooncol. 2013 Oct 27.

●● Enlace al texto completo (gratis o de pago) [1007/s11060-013-1292-2](#)

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**INSTITUCIÓN / INSTITUTION:** - School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong, China.

**RESUMEN / SUMMARY:** - The purpose of the present study was to evaluate the anti-tumor effects of 18beta-glycyrrhetic acid (GA), a natural compound extracted from liquorice, against pituitary adenoma and its underlying mechanisms in cultured cells and mouse model of xenografted tumor. GA induced cellular damage in rat pituitary adenoma-derived MMQ and GH3 cells, manifested as reduced cell viability, increased lactate dehydrogenase release, elevated intracellular reactive oxygen species (ROS) and Ca<sup>2+</sup> concentration. GA also caused G<sub>0</sub>/G<sub>1</sub> phase arrest, increased apoptosis rate and increased mitochondrial membrane permeabilization by suppressing the mitochondrial membrane potential and down-regulating a ratio of B cell lymphoma 2 (Bcl-2) and Bax. GA activated calcium/calmodulin-dependent protein kinase II (CaMKII), c-Jun N-terminal kinase (JNK) and P38; but these activating effects were attenuated by pretreatment with N-acetyl-L-cysteine, a ROS inhibitor. Pretreatment with KN93, a CaMKII inhibitor, also abolished the GA activation of JNK and P38. GA remarkably inhibited growth of pituitary adenoma grafted on nude mice. These results suggest that the anti-pituitary adenoma effect of GA is associated with its apoptotic actions by activating mitochondria-mediated ROS/mitogen-activated protein kinase pathways in particular CaMKII that may serve a linkage between ROS accumulation and the activation of JNK and P38. This study provides experimental evidence in the support of further developing GA as a chemotherapeutic agent for pituitary adenoma.

[483]

**TÍTULO / TITLE:** - The seed and soil hypothesis revisited: Current state of knowledge of inherited genes on prognosis in breast cancer.

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

**REVISTA / JOURNAL:** - Cancer Treat Rev. 2014 Mar;40(2):293-9. doi: 10.1016/j.ctrv.2013.09.010. Epub 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1016/j.ctrv.2013.09.010](#)

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**RESUMEN / SUMMARY:** - The crucial event in the course of malignancies such as breast cancer is its metastatic spread from the primary tumor of origin to distant organs. The natural history of a tumor is determined by the expression of its genes, and in this sense, knowledge has advanced dramatically in recent decades. However, much less is known about the role that the patient plays in the behavior of a tumor. In this article, we review the evidence regarding the genetic background of the host in metastatic tumor dissemination, providing information from epidemiological studies as well as from animal models and human studies. Undoubtedly, the elucidation of possible interpersonal variability in susceptibility to developing metastases would significantly contribute to improve management of cancer patients.

[484]

**TÍTULO / TITLE:** - Sodium meta-arsenite induces reactive oxygen species-dependent apoptosis, necrosis, and autophagy in both androgen-sensitive and androgen-insensitive prostate cancer cells.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2014 Jan;25(1):53-62. doi: 10.1097/CAD.000000000000013.

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

[1097/CAD.000000000000013](#)

**AUTORES / AUTHORS:** - Kim Y; Jeong IG; You D; Song SH; Suh N; Jang SW; Kim S; Hwang JJ; Kim CS

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**RESUMEN / SUMMARY:** - Sodium meta-arsenite (NaAsO<sub>2</sub>), a novel compound synthesized by Komipharm International Co. Ltd, is an orally bioavailable, water-soluble trivalent arsenical that has shown potent cytotoxic activity in human solid cancer cells in vitro and in vivo, and is currently undergoing phase I/II clinical trials for the treatment of prostate cancer. In this study, mechanisms of cell death induced by sodium meta-arsenite were investigated. Sodium meta-arsenite reduced cell viability and increased the sub-G1 population in cell cycle analysis in both androgen-sensitive LNCaP and androgen-insensitive CWR22RV1 cells. The apoptosis induced by sodium meta-arsenite was associated with cleavage of caspases 3, 8, and 9, and poly (ADP-ribose) polymerase (PARP) and increased annexin V-positive cells, and was inhibited by the pan-caspase inhibitor Z-VAD-fmk. Sodium meta-arsenite also increased the level of the autophagy marker microtubule-associated protein 1 light chain 3 (LC3)-II and the number of autophagic vacuoles as shown by electron microscopy. Both the autophagy inhibitor 3-methyladenine and the necrosis inhibitor necrostatin-1 blocked cell death induced by sodium meta-arsenite. Moreover, sodium meta-arsenite led to the accumulation of intracellular reactive oxygen species (ROS) and N-acetyl-L-cysteine (NAC), a ROS scavenger, decreased sodium meta-arsenite-induced levels of cleaved PARP and LC3-II. Propidium iodide (PI) staining also showed that NAC restored membrane integrity, damaged by sodium meta-arsenite. Therefore, these results suggest that sodium meta-arsenite induces apoptotic, necrotic, and autophagic cell

death through intracellular ROS accumulation in both androgen-sensitive and androgen-insensitive prostate cancer cells and may be used as a new anticancer drug for the treatment of prostate cancer.

[485]

**TÍTULO / TITLE:** - Oxymatrine induces apoptosis in human cervical cancer cells through guanine nucleotide depletion.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Nov 14.

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

[1097/CAD.0000000000000012](#)

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**RESUMEN / SUMMARY:** - Oxymatrine is an alkaloid obtained primarily from Sophora roots and has been shown to show anticancer effects in various cancers. However, the cellular and molecular effects of this agent on cervical cancer have been poorly characterized. Here, we investigated the antitumor effect of oxymatrine on a human cervical cancer cell line (HeLa). Our results showed that application of oxymatrine significantly inhibited the cell growth and tumorigenesis in a dose-dependent manner and induced apoptosis through caspase-dependent pathways as determined using flow cytometry and TUNEL staining analysis. To define the proteins potentially related to the mechanisms of action, proteomic analysis was utilized to detect proteins altered by oxymatrine. As the downregulated gene, inosine monophosphate dehydrogenase type II (IMPDH2) was responsible for oxymatrine-induced mitochondrial-related apoptosis. Moreover, oxymatrine depleted intracellular guanosine 5'-triphosphate (GTP) levels by effective IMPDH inhibition. Functional analyses further showed that oxymatrine and tiazofurin, an inhibitor of IMPDH2, sensitized resistant HeLa/DDP cells to cisplatin. In addition, the expression of IMPDH2 in cervical cancer was significantly higher than that in the normal cervical epithelium. Taken together, these findings suggest that targeting of IMPDH2 by potential pharmacological inhibitors, oxymatrine in combination with chemotherapy, might be a promising means of overcoming chemoresistance in cervical cancer with high IMPDH2 expression, and may thus provide new insights into the mechanism of oxymatrine-induced anticancer effects.

[486]

**TÍTULO / TITLE:** - Serum vascular adhesion protein-1 predicts all-cause mortality and cancer-related mortality in subjects with colorectal cancer.

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

**REVISTA / JOURNAL:** - Clin Chim Acta. 2013 Nov 7;428C:51-56. doi: 10.1016/j.cca.2013.10.024.

●● Enlace al texto completo (gratis o de pago) [1016/j.cca.2013.10.024](#)

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**RESUMEN / SUMMARY:** - BACKGROUND: Vascular adhesion protein-1 (VAP-1) participates in inflammation and catalyzes the breakdown of amines to produce aldehyde, hydrogen peroxide, and ammonia. Serum VAP-1 can predict cancer mortality, including colorectal cancer (CRC) mortality, in type 2 diabetic subjects. However, it remains unknown if serum VAP-1 can predict mortality in CRC patients. This prospective cohort study investigates if serum VAP-1 is a novel biomarker for mortality prediction in CRC. METHODS: We enrolled 300 CRC patients. Preoperative serum VAP-1 was measured by time-resolved immunofluorometric assay. They were followed until September 2009 or death, which was ascertained by the National Death Registration System. RESULTS: The median follow-up period was 4.7 years. Compared with normal counterpart, VAP-1 immunoactivity was upregulated in CRC tissues, especially at the invasion front. Serum VAP-1 can independently predict all-cause mortality (HR: 1.0026, 95% CI: 1.0003-1.0050, P<0.05) and cancer-related mortality (HR: 1.0026, 95% CI: 1.0001-1.0050, P<0.05). A risk score composed of age, gender, carcinoembryonic antigen (CEA) >5ng/ml, tumor grading, tumor staging, and serum VAP-1 could stratify CRC patients into low-, intermediate-, and high-risk subgroups, with a 5-year mortality rate of 10%, 34%, and 78%, respectively. CONCLUSIONS: Serum VAP-1 predicts mortality independently and improves risk stratification in CRC subjects.

[487]

**TÍTULO / TITLE:** - Growth inhibition by novel liposomes including trehalose surfactant against hepatocarcinoma cells along with apoptosis.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):4727-40.

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**RESUMEN / SUMMARY:** - Novel liposomes composed of L-alpha-dimyristoylphosphatidylcholine (DMPC) and trehalose surfactant (DMTreCn) were produced by the method of sonication in buffer solution. The thickness of fixed aqueous layer of DMTreCn was larger than that of DMPC liposomes and increased in a dose-dependent manner. The remarkable inhibitory effects of DMTreCn on the growth of human hepatocellular carcinoma (HCC) (Hep-G2 and HuH-7) cells were obtained along with apoptosis, without affecting the growth of normal cells. DMTreCn induced apoptosis of Hep-G2 and HuH-7 cells through the activation of caspase-3, 8 and 9. Release of cytochrome c from mitochondria and activation of Bcl-2 family protein (BAX) were recorded, indicating that DMTreCn induced apoptosis of Hep-G2 and HuH-7 cells through mitochondrial pathway via BAX. It is noteworthy that the remarkable inhibitory effects of DMTreCn on the growth of human HCC cells were obtained along with apoptosis for the first time.

[488]

**TÍTULO / TITLE:** - Id4 promotes senescence and sensitivity to doxorubicin-induced apoptosis in DU145 prostate cancer cells.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4271-8.

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**RESUMEN / SUMMARY:** - Inhibitor of differentiation proteins (Id1, 2, 3 and 4) are dominant negative regulators of basic helix loop helix transcription factors and play dominant roles in cancer cells, spanning several molecular pathways including senescence, invasion, metastasis, proliferation and apoptosis. In contrast to high Id1, Id2 and Id3 expression, the expression of Id4 is epigenetically silenced in prostate cancer. In the present study we demonstrated a novel role of Id4, that of promotion of cellular senescence in prostate cancer cells. **MATERIALS AND METHODS:** Id4 was ectopically expressed in DU145 cells (DU145+Id4). The cells treated with Doxorubicin (0-500 nm) or vehicle control were analyzed for apoptosis, senescence (SA-beta Galactosidase), and expression of CDKN1A (p21), CDKN1B(p27), CDKN2A (p16), E2F1, vimentin and E-cadherin by immuno-histochemistry and/or Western blot. **RESULTS:** In the present study we demonstrated that Id4 promotes cellular senescence in prostate cancer cell line DU145. Ectopic overexpression of Id4 in androgen receptor-negative DU145 prostate cancer cells resulted in increased expression of p16, p21, p27, E-cadherin and vimentin but down-regulated E2F1 expression. Id4 also potentiated the effect of doxorubicin induced senescence and apoptosis. **CONCLUSION:** The absence of functional p16, pRB and p53 in DU145 suggests that Id4 could alter additional molecular pathways such as those involving E2F1 to promote senescence and increased sensitivity to doxorubicin-induced apoptosis. The results of the present study support the role of Id4 as a tumor suppressor in prostate cancer.

[489]

**TÍTULO / TITLE:** - A gene expression profile related to immune dampening in the tumor microenvironment is associated with poor prognosis in gastric adenocarcinoma.

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

**REVISTA / JOURNAL:** - J Gastroenterol. 2013 Nov 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00535-013-0904-0](#)

**AUTORES / AUTHORS:** - Pasini FS; Zilberstein B; Snitcovsky I; Roela RA; Mangone FR; Ribeiro U Jr; Nonogaki S; Brito GC; Callegari GD; Cecconello I; Alves VA; Eluf-Neto J; Chammas R; Federico MH

**INSTITUCIÓN / INSTITUTION:** - Departamento de Radiologia e Oncologia, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil.

**RESUMEN / SUMMARY:** - **BACKGROUND:** The TNM Classification of Malignant Tumours (TNM) staging system is the primary means of determining a prognosis for gastric adenocarcinoma (GC). However, tumor behavior in the individual patient is unpredictable and in spite of treatment advances, a classification of 'advanced stage'

still portends a poor prognosis. Thus, further insights from molecular analyses are needed for better prognostic stratification and determination of new therapeutic targets. METHODS: A total of fifty-one fresh frozen tumor samples from patients with histopathologically confirmed diagnoses of GC, submitted to surgery with curative intent, were included in the study. Total RNA was extracted from an initial group of fifteen samples matched for known prognostic factors, categorized into two subgroups, according to patient overall survival: poor (<24 months) or favorable (at or above 24 months), and hybridized to Affymetrix Genechip human genome U133 plus 2.0 for genes associated with prognosis selection. Thirteen genes were selected for qPCR validation using those initial fifteen samples plus additional thirty-six samples. RESULTS: A total of 108 genes were associated with poor prognosis, independent of tumor staging. Using systems biology, we suggest that this panel reflects the dampening of immune/inflammatory response in the tumor microenvironment level and a shift to Th2/M2 activity. A gene trio (OLR1, CXCL11 and ADAMDEC1) was identified as an independent marker of prognosis, being the last two markers validated in an independent patient cohort. CONCLUSIONS: We determined a panel of three genes with prognostic value in gastric cancer, which should be further investigated. A gene expression profile suggestive of a dysfunctional inflammatory response was associated with unfavorable prognosis.

[490]

**TÍTULO / TITLE:** - MicroRNA-23a is involved in tumor necrosis factor-alpha induced apoptosis in mesenchymal stem cells and myocardial infarction.

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

**REVISTA / JOURNAL:** - Exp Mol Pathol. 2013 Nov 19. pii: S0014-4800(13)00139-1. doi: 10.1016/j.yexmp.2013.11.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.yexmp.2013.11.005](#)

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**RESUMEN / SUMMARY:** - Cell therapy has emerged as an attractive therapeutic modality to treat myocardial infarction (MI) via repairing damaged myocardium, and mesenchymal stem cells (MSCs) are an appealing therapeutic approach for cardiac regeneration. However, the clinical application of MSC-based therapy is restricted because of the poor survival of implanted cells, and this poor survival remains poorly understood. Using a tumor necrosis factor (TNF)-alpha-induced bone marrow (BM)-MSC injury model in vitro and a rat MI model in vivo, we showed in the current study that miR-23a was involved in TNF-alpha-induced BM-MSC apoptosis through regulating caspase-7 and that the injection of BM-MSCs overexpressing miR-23a could improve left ventricular (LV) function and reduce infarct size in the rat MI model. Our findings elucidate the etiology of MI and provide an alternative treatment strategy for patients with heart failure caused by MI who are not optimal candidates for surgical treatment.

[491]

**TÍTULO / TITLE:** - Characterization of WZ4003 and HTH-01-015 as selective inhibitors of the LKB1 tumour suppressor activated NUAK kinases.

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

**REVISTA / JOURNAL:** - Biochem J. 2013 Oct 30.

●● Enlace al texto completo (gratis o de pago) [1042/BJ20131152](#)

**AUTORES / AUTHORS:** - Banerjee S; Buhrlage SJ; Huang HT; Deng X; Zhou W; Wang J; Traynor R; Prescott AR; Alessi DR; Gray NS

**RESUMEN / SUMMARY:** - The NUAK1 and NUAK2 are members of the AMPK family of protein kinase that are activated by the LKB1 tumour suppressor kinase. Recent work suggests they play roles in regulating key biological processes including Myc driven tumorigenesis, senescence, cell adhesion and neuronal polarity. We describe the first highly specific protein kinase inhibitors of NUAK kinases namely WZ4003 and HTH-01-015. WZ4003 inhibits both NUAK isoforms, whereas HTH-01-015 inhibits only NUAK1. These compounds display extreme selectivity and do not significantly inhibit the activity of 139 other kinases tested including 10 AMPK family members. WZ4003 and HTH-01-015 inhibit the phosphorylation of the only well-characterised substrate namely MYPT1 that is phosphorylated by NUAK1 at Ser445. We identify a mutation that does not affect basal NUAK1 activity but renders it resistant to both WZ4003 and HTH-01-015.

Consistent with NUAK1 mediating phosphorylation of MYPT1 we find that in cells overexpressing drug resistant NUAK1, but not wild type NUAK1, phosphorylation of MYPT1 at Ser445 is no longer suppressed by WZ4003 or HTH-01-015. We also demonstrate that administration of WZ4003 and HTH-01-015 to mouse embryonic fibroblasts (MEFs) significantly inhibits migration in a wound-healing assay to a similar extent as NUAK1 knock-out. WZ4003 and HTH-01-015 also inhibit proliferation of MEFs to the same extent as NUAK1 knockout and U2OS cells to the same extent as NUAK1 shRNA knock-down. WZ4003 and HTH-01-015 impaired the invasive potential of U2OS cells in a 3D cell invasion assay to the same extent as NUAK1 knock-down. Our data indicate that WZ4003 and HTH-01-015 will serve as useful chemical probes to delineate the biological roles of the NUAKs .

[492]

**TÍTULO / TITLE:** - Association between interleukin-4 -590C > T polymorphism and non-Hodgkin's lymphoma risk.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 23.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1394-7](#)

**AUTORES / AUTHORS:** - Zhou C; Cui S; Zhou R; Dou L

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Binzhou Medical University Hospital, 661 Huangheer Road, Binzhou, 256603, Shandong, China.

**RESUMEN / SUMMARY:** - Many studies were performed to assess the association between IL-4 -590C > T polymorphism and non-Hodgkin's lymphoma (NHL) risk, but no consensus was available up to now. We conducted a meta-analysis to examine the association between IL-4 -590C > T polymorphism and NHL risk. We used odds ratios (ORs) to assess the strength of the association and 95 % confidence intervals (CIs) to give a sense of the precision of the estimate. A total of six studies were found to be eligible for meta-analyses of IL-4 -590C > T variant. Results from this study showed

that IL-4 -590C > T polymorphism was not significantly associated with NHL risk under all genetic models in overall population. Further sensitivity analysis confirmed the results. In subgroup analyses stratified by race, no significant association was found in either Caucasian or mixed populations. The meta-analysis indicated that elected -590C > T polymorphism of IL-4 may not be a risk factor for NHL development.

[493]

**TÍTULO / TITLE:** - Exploring the potential of [11C]choline-PET/CT as a novel imaging biomarker for predicting early treatment response in prostate cancer.

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

**REVISTA / JOURNAL:** - Nucl Med Commun. 2014 Jan;35(1):20-9. doi: 10.1097/MNM.0000000000000014.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1097/MNM.0000000000000014](#)

**AUTORES / AUTHORS:** - Challapalli A; Barwick T; Tomasi G; O' Doherty M; Contractor K; Stewart S; Al-Nahas A; Behan K; Coombes C; Aboagye EO; Mangar S

**INSTITUCIÓN / INSTITUTION:** - Departments of aSurgery and Cancer bRadiology/Nuclear Medicine, Imperial College London and Imperial College Healthcare NHS Trust cThe PET Imaging Centre, St Thomas' Hospital, London, UK.

**RESUMEN / SUMMARY:** - **OBJECTIVES:** The aim of the study was to assess the effects of neoadjuvant androgen deprivation (NAD) and radical prostate radiotherapy with concurrent androgen deprivation (RT-CAD) on prostatic [C]choline kinetics and thus develop methodology for the use of [C]choline-PET/computed tomography (CT) as an early imaging biomarker. **MATERIALS AND METHODS:** Ten patients with histologically confirmed prostate cancer underwent three sequential dynamic [C]choline-PET/CT pelvic scans: at baseline, after NAD and 4 months after RT-CAD. [C]Choline uptake was quantified using the average and maximum standardized uptake values at 60 min (SUV60,ave and SUV60,max), the tumour-to-muscle ratios (TMR60,max) and net irreversible retention of [C]choline at steady state (Kimod-pat). **RESULTS:** The combination of NAD and RT-CAD significantly decreased tumour [C]choline uptake (SUV60,ave, SUV60,max, TMR60,max or Kimod-pat) and prostate-specific antigen (PSA) levels (analysis of variance,  $P < 0.001$  for all variables). Although the magnitude of reduction in the variables was larger after NAD, there was a smaller additional reduction after RT-CAD. A wide range of reduction in tumour SUV60,ave (38-83.7%) and SUV60,max (22.2-85.3%) was seen with combined NAD and RT-CAD despite patients universally achieving PSA suppression (narrow range of 93.5-99.7%). There was good association between baseline SUV60,max and initial PSA levels (Pearson's  $r = 0.7$ ,  $P = 0.04$ ). The reduction in tumour SUV60,ave after NAD was associated with PSA reduction ( $r = 0.7$ ,  $P = 0.04$ ). This association occurred despite the larger reduction in PSA (94%) compared with SUV60,ave (58%). **CONCLUSION:** This feasibility study shows that [C]choline-PET/CT detects metabolic changes within tumours following NAD and RT-CAD to the prostate. A differential reduction in [C]choline uptake despite a global reduction in PSA following NAD and RT-CAD could provide prognostic information and warrants further evaluation as an imaging biomarker in this setting.

[494]

**TÍTULO / TITLE:** - Interleukin-7 Mediates Selective Expansion of Tumor-redirected Cytotoxic T Lymphocytes (CTLs) without Enhancement of Regulatory T-cell Inhibition.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-](#)

[1016](#)

**AUTORES / AUTHORS:** - Perna SK; Pagliara D; Mahendravada A; Liu H; Brenner MK; Savoldo B; Dotti G

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Center for Cell and Gene Therapy, and Departments of Pediatrics, Immunology, and Medicine, Baylor College of Medicine, Methodist Hospital and Texas Children's Hospital, Houston, Texas; Dipartimento di Ematologia ed Oncologia Pediatrica, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy.

**RESUMEN / SUMMARY:** - **PURPOSE:** The antitumor activity of chimeric antigen receptor (CAR)-redirected CTLs should be enhanced if it were possible to increase their proliferation and function after adoptive transfer without concomitantly increasing the proliferation and function of regulatory T cells (Treg). Here, we explored whether the lack of IL-7Ralpha in Treg can be exploited by the targeted manipulation of the interleukin-7 (IL-7) cytokine-cytokine receptor axis in CAR-engrafted Epstein-Barr Virus-specific CTLs (EBV-CTLs) to selectively augment their growth and antitumor activity even in the presence of Treg. **EXPERIMENTAL DESIGN:** We generated a bicistronic retroviral vector encoding a GD2-specific CAR and the IL-7Ralpha subunit, expressed the genes in EBV-CTLs, and assessed their capacity to control tumor growth in the presence of Treg in vitro and in vivo when exposed to either interleukin-2 (IL-2) or IL-7 in a neuroblastoma xenograft. **RESULTS:** We found that IL-7, in sharp contrast with IL-2, supports the proliferation and antitumor activity of IL-7Ralpha.CAR-GD2+ EBV-CTLs both in vitro and in vivo even in the presence of fully functional Treg. **CONCLUSIONS:** IL-7 selectively favors the survival, proliferation, and effector function of IL-7Ralpha-transgenic/CAR-redirected EBV-CTLs in the presence of Treg both in vitro and in vivo. Thus, IL-7 can have a significant impact in sustaining expansion and persistence of adoptively CAR-redirected CTLs. Clin Cancer Res; 1-9. ©2013 AACR.

[495]

**TÍTULO / TITLE:** - Inhibition of c-Met promoted apoptosis, autophagy and loss of the mitochondrial transmembrane potential in oridonin-induced A549 lung cancer cells.

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

**REVISTA / JOURNAL:** - J Pharm Pharmacol. 2013 Nov;65(11):1622-42. doi: 10.1111/jphp.12140. Epub 2013 Sep 15.

●● Enlace al texto completo (gratis o de pago) [1111/jphp.12140](#)

**AUTORES / AUTHORS:** - Liu Y; Liu JH; Chai K; Tashiro S; Onodera S; Ikejima T

**INSTITUCIÓN / INSTITUTION:** - Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, China; China-Japan Research Institute of Medical and Pharmaceutical Sciences, Shenyang Pharmaceutical University, Shenyang, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: Herein, inhibition of hepatocyte growth factor receptor, c-Met, significantly increased cytochrome c release and Bax/Bcl-2 ratio, indicating that c-Met played an anti-apoptotic role. The following experiments are to elucidate this anti-apoptotic mechanism, then the effect of c-Met on autophagy has also been discussed. METHODS: Investigated was the influence of c-Met on apoptosis, autophagy and loss of mitochondrial transmembrane potential (Deltapsim), and the relevant proteins were examined. KEY FINDINGS: First, we found that activation of extracellular signal-regulated kinase (ERK), p53 was promoted by c-Met interference. Subsequent studies indicated that ERK was the upstream effector of p53, and this ERK-p53 pathway mediated release of cytochrome c and up-regulation of Bax/Bcl-2 ratio. Secondly, the inhibition of c-Met augmented oridonin-induced loss of mitochondrial transmembrane potential (Deltapsim), resulting apoptosis. Finally, the inhibition of c-Met increased oridonin-induced A549 cell autophagy accompanied by Beclin-1 activation and conversion from microtubule-associated protein light chain 3 (LC3)-I to LC3-II. Activation of ERK-p53 was also detected in autophagy process and could be augmented by inhibition of c-Met. Moreover, suppression of autophagy by 3-methyladenine (3-MA) or small interfering RNA against Beclin-1 or Atg5 decreased oridonin-induced apoptosis. Inhibition of apoptosis by pan-caspase inhibitor (z-VAD-fmk) decreased oridonin-induced autophagy as well and Loss of Deltapsim also occurred during autophagic process. CONCLUSION: Thus, inhibiting c-Met enhanced oridonin-induced apoptosis, autophagy and loss of Deltapsim in A549 cells.

[496]

**TÍTULO / TITLE:** - Nickel oxide nanoparticles exert cytotoxicity via oxidative stress and induce apoptotic response in human liver cells (HepG2).

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

**REVISTA / JOURNAL:** - Chemosphere. 2013 Nov;93(10):2514-22. doi: 10.1016/j.chemosphere.2013.09.047. Epub 2013 Oct 15.

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

[1016/j.chemosphere.2013.09.047](http://1016/j.chemosphere.2013.09.047)

**AUTORES / AUTHORS:** - Ahamed M; Ali D; Alhadlaq HA; Akhtar MJ

**INSTITUCIÓN / INSTITUTION:** - King Abdullah Institute for Nanotechnology, King Saud University, Riyadh 11451, Saudi Arabia. Electronic address: [maqsood@gmail.com](mailto:maqsood@gmail.com).

**RESUMEN / SUMMARY:** - Increasing use of nickel oxide nanoparticles (NiO NPs) necessitates an improved understanding of their potential impact on human health. Previously, toxic effects of NiO NPs have been investigated, mainly on airway cells. However, information on effect of NiO NPs on human liver cells is largely lacking. In this study, we investigated the reactive oxygen species (ROS) mediated cytotoxicity and induction of apoptotic response in human liver cells (HepG2) due to NiO NPs exposure. Prepared NiO NPs were crystalline and spherical shaped with an average diameter of 44nm. NiO NPs induced cytotoxicity (cell death) and ROS generation in HepG2 cells in dose-dependent manner. Further, ROS scavenger vitamin C reduced cell death drastically caused by NiO NPs exposure indicating that oxidative stress plays an important role in NiO NPs toxicity. Micronuclei induction, chromatin condensation and DNA damage in HepG2 cells treated with NiO NPs suggest that NiO NPs induced cell death via apoptotic pathway. Quantitative real-time PCR analysis showed that following the exposure of HepG2 cells to NiO NPs, the expression level of mRNA of

apoptotic genes (bax and caspase-3) were up-regulated whereas the expression level of anti-apoptotic gene bcl-2 was down-regulated. Moreover, activity of caspase-3 enzyme was also higher in NiO NPs treated cells. To the best of our knowledge this is the first report demonstrating that NiO NPs caused cytotoxicity via ROS and induced apoptosis in HepG2 cells, which is likely to be mediated through bax/bcl-2 pathway. This work warrants careful assessment of Ni NPs before their commercial and industrial applications.

[497]

**TÍTULO / TITLE:** - A novel laccase with inhibitory activity towards HIV-I reverse transcriptase and antiproliferative effects on tumor cells from the fermentation broth of mushroom *Pleurotus cornucopiae*.

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

**REVISTA / JOURNAL:** - Biomed Chromatogr. 2013 Oct 18. doi: 10.1002/bmc.3068.

●● Enlace al texto completo (gratis o de pago) [1002/bmc.3068](#)

**AUTORES / AUTHORS:** - Wu X; Huang C; Chen Q; Wang H; Zhang J

**INSTITUCIÓN / INSTITUTION:** - Institute of Agricultural Resources and Regional Planning, Chinese Academy of Agricultural Sciences, 12 Zhongguancun South Street, Beijing, 100081, China; State Key Laboratory for Agrobiotechnology and Department of Microbiology, China Agricultural University, 2 Yuanmingyuan Westroad, Beijing, 100193, China.

**RESUMEN / SUMMARY:** - A novel laccase with a molecular mass of 67 kDa was isolated from the fermentation broth of *Pleurotus cornucopiae* through ion exchange chromatography and gel filtration. The optimal pH and temperature for the laccase was pH 4.2 and 30 degrees C, respectively. The laccase activity was remarkably inhibited by Fe<sup>3+</sup> and Hg<sup>2+</sup>, while it was stimulated by Cu<sup>2+</sup> and Pb<sup>2+</sup>. It inhibited proliferation of the hepatoma cells HepG2 and the breast cancer cells MCF-7, and the activity of HIV-I reverse transcriptase with IC<sub>50</sub> values of 3.9, 7.6 and 3.7 μM, respectively. Copyright © 2013 John Wiley & Sons, Ltd.

[498]

**TÍTULO / TITLE:** - Prognostic value of fibroblast growth factor receptor 1 gene locus amplification in resected lung squamous cell carcinoma.

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

**REVISTA / JOURNAL:** - J Thorac Oncol. 2013 Nov;8(11):1371-7. doi: 10.1097/JTO.0b013e3182a46fe9.

●● Enlace al texto completo (gratis o de pago) [1097/JTO.0b013e3182a46fe9](#)

**AUTORES / AUTHORS:** - Craddock KJ; Ludkovski O; Sykes J; Shepherd FA; Tsao MS

**INSTITUCIÓN / INSTITUTION:** - \*Departments of Pathology, daggerOntario Cancer Institute, double daggerDepartment of Biostatistics, section signDivision of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; and paragraph signDepartments of Laboratory Medicine and Pathobiology, ||Medicine, University of Toronto, Ontario, Canada.

**RESUMEN / SUMMARY:** - INTRODUCTION: Fibroblast growth factor receptor 1 (FGFR1) gene amplification was recently reported as a recurrent abnormality in 10% to 20% of primary lung squamous cell carcinomas (SqCCs), and has attracted

significant interest as a potential therapeutic target. Limited data are available for its prognostic impact in early-stage SqCC. METHODS: Tissue microarrays containing 135 primary lung SqCCs and 58 matching lymph node metastases were tested by interphase fluorescence in situ hybridization for DNA copy number (CN) abnormalities at the 8p12 region including FGFR1. RESULTS: FGFR1 amplification was found in 18.2% (22 of 121 evaluable) of primary SqCC, using a definition of average copies of FGFR1 per cell of 5.0 or more. Concordance rate between primaries and matching lymph node metastases was 97.7% (43 of 44; 7 amplified and 37 nonamplified), with the only discordant case showing CN at approximately the dichotomous cutoff. Similarly, concordance between two separate lymph node metastases in each of 10 patients was 100% (1 amplified and 9 nonamplified). Using various CN cutoffs, we found no statistically significant association between FGFR1 CN abnormalities and patient age, sex, tumor grade, stage, smoking status, disease-free survival, cause-specific survival, or overall survival. CONCLUSION: FGFR1 amplification is not prognostic in resected lung squamous cell carcinoma patients.

[499]

**TÍTULO / TITLE:** - Ziv-aflibercept: a novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer.

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

**REVISTA / JOURNAL:** - Am J Health Syst Pharm. 2013 Nov 1;70(21):1887-96. doi: 10.2146/ajhp130143.

●● [Enlace al texto completo \(gratis o de pago\) 2146/ajhp130143](#)

**AUTORES / AUTHORS:** - Chung C; Pherwani N

**INSTITUCIÓN / INSTITUTION:** - Clement Chung, Pharm.D., BCOP, BCPS, is Oncology Clinical Pharmacist, Lyndon B. Johnson General Hospital, Harris Health System, Houston, TX. Nisha Pherwani, Pharm.D., BCOP, is Clinical Director, Oncology, Cardinal Health Pharmacy Solutions, Houston, TX 77077.

**RESUMEN / SUMMARY:** - PURPOSE: The pharmacology, pharmacokinetics, clinical efficacy, safety, and administration of ziv-aflibercept in combination therapy for metastatic colorectal cancer (mCRC) are reviewed. SUMMARY: Ziv-aflibercept (Zaltrap, Regeneron Pharmaceuticals and sanofi-aventis) is a novel recombinant fusion protein that targets the angiogenesis signaling pathway of tumor cells by blocking vascular endothelial growth factor (VEGF) receptors that play a key role in tumor growth and metastasis; it is a more potent VEGF blocker than bevacizumab. Ziv-aflibercept is approved by the Food and Drug Administration for use in combination with fluorouracil, irinotecan, and leucovorin (the FOLFIRI regimen) for second-line treatment of patients with mCRC who have disease progression during first-line oxaliplatin-based chemotherapy. A Phase III trial demonstrated that relative to FOLFIRI therapy alone, the use of ziv-aflibercept was associated with significantly improved patient response, overall survival, and progression-free survival in patients with good performance status at baseline, including some who had received prior bevacizumab therapy. The most common grade 3 or 4 adverse effects associated with ziv-aflibercept use in clinical studies were neutropenia, hypertension, and diarrhea; the U.S. product labeling warns of potential hemorrhage and other treatment-related risks.

CONCLUSION: Current clinical data are insufficient to directly compare ziv-aflibercept and bevacizumab when used with standard combination chemotherapy as first- or

second-line regimens for mCRC. The role of ziv-aflibercept is currently limited to the second-line setting in combination with irinotecan-based regimens in mCRC patients who have not received irinotecan previously. The role of ziv-aflibercept in chemotherapy for other tumor types is yet to be determined.

[500]

**TÍTULO / TITLE:** - Src Family Kinase Inhibition as a Novel Strategy to Augment Melphalan-Based Regional Chemotherapy of Advanced Extremity Melanoma.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Nov 27.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3387-6](#)

**AUTORES / AUTHORS:** - Tokuhisa Y; Lidsky ME; Toshimitsu H; Turley RS; Beasley GM; Ueno T; Sharma K; Augustine CK; Tyler DS

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Duke University Medical Center, Durham, NC, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Src kinase inhibition has been shown to augment the efficacy of chemotherapy. Dasatinib, a dual Src/Abl kinase inhibitor approved for the treatment of CML, is under investigation as monotherapy for tumors with abnormal Src signaling, such as melanoma. The goal of this study was to determine if Src kinase inhibition using dasatinib could enhance the efficacy of regionally administered melphalan in advanced extremity melanoma. METHODS: The mutational status of c-kit and patterns of gene expression predictive of dysregulated Src kinase signaling were evaluated in a panel of 26 human melanoma cell lines. The effectiveness of dasatinib was measured by quantifying protein expression and activation of Src kinase, focal adhesion kinase, and Crk-associated substrate (p130CAS), in conjunction with in vitro cell viability assays using seven melanoma cell lines. Utilizing a rat model of regional chemotherapy, we evaluated the effectiveness of systemic dasatinib in conjunction with regional melphalan against the human melanoma cell line, DM443, grown as a xenograft. RESULTS: Only the WM3211 cell line harbored a c-kit mutation. Significant correlation was observed between Src-predicted dysregulation by gene expression and sensitivity to dasatinib in vitro. Tumor doubling time for DM443 xenografts treated with systemic dasatinib in combination with regional melphalan (44.8 days) was significantly longer ( $p = 0.007$ ) than either dasatinib (21.3 days) or melphalan alone (24.7 days). CONCLUSIONS: Systemic dasatinib prior to melphalan-based regional chemotherapy markedly improves the efficacy of this alkylating agent in this melanoma xenograft model. Validation of this concept should be considered in the context of a regional therapy clinical trial.

[501]

**TÍTULO / TITLE:** - Oral mucosal injury caused by cancer therapies: current management and new frontiers in research.

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

**REVISTA / JOURNAL:** - J Oral Pathol Med. 2013 Nov 22. doi: 10.1111/jop.12135.

●● Enlace al texto completo (gratis o de pago) [1111/jop.12135](#)

**AUTORES / AUTHORS:** - Jensen SB; Peterson DE

**INSTITUCIÓN / INSTITUTION:** - Section of Oral Medicine, Clinical Oral Physiology, Oral Pathology & Anatomy, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

**RESUMEN / SUMMARY:** - This invited update is designed to provide a summary of the state-of-the-science regarding oral mucosal injury (oral mucositis) caused by conventional and emerging cancer therapies. Current modeling of oral mucositis pathobiology as well as evidence-based clinical practice guidelines for prevention and treatment of oral mucositis are presented. In addition, studies addressing oral mucositis as published in the Journal of Oral Pathology and Medicine 2008-2013 are specifically highlighted in this context. Key research directions in basic and translational science associated with mucosal toxicity caused by cancer therapies are also delineated as a basis for identifying pathobiologic and pharmacogenomic targets for interventions. This collective portfolio of research and its ongoing incorporation into clinical practice is setting the stage for the clinician in the future to predict mucosal toxicity risk and tailor therapeutic interventions to the individual oncology patient accordingly.

[502]

**TÍTULO / TITLE:** - Ovarian Cancer in BRCA Mutation Carriers: Improved Outcome After Intraperitoneal (IP) Cisplatin.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3277-y](#)

**AUTORES / AUTHORS:** - Kwa M; Edwards S; Downey A; Reich E; Wallach R; Curtin J; Muggia F

**INSTITUCIÓN / INSTITUTION:** - New York University Medical Center, NYU Cancer Institute, New York, NY, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Ovarian cancer arising in women with BRCA mutations is known to have a more favorable outcome and to be more responsive to platinum-based regimens than in those without a hereditary background. We analyze our previously published intraperitoneal (IP) studies in relation to BRCA mutation status and update their outcomes. METHODS: Among 62 patients with ovarian cancer enrolled in IP platinum doublet studies in clinical trials (with etoposide (n = 18), with floxuridine (n = 30), and with topotecan (n = 14)), a deleterious BRCA mutation was eventually identified in 10 patients. The outcomes in these BRCA mutation carriers are described and compared with survival of others in respective trials. RESULTS: Ten patients that were confirmed to have BRCA mutations-all with high-grade and stages IIC to IV disease-survived a median of 10 years (range: 4-18+) after receiving IP cisplatin-based regimens. Two continue with no evidence of disease since their IP treatment, while four others remain alive with recurrences after 8, 9, 10, and 11 years, respectively. CONCLUSIONS: This experience suggests that IP cisplatin leads to favorable long term outcomes in advanced ovarian cancer in women with defective homologous recombination (i.e., with deleterious BRCA mutations). Whether such cisplatin dose-intensification from IP relative to (intravenous) IV drug administration leads to superior results in these mutation carriers requires further study.

[503]

**TÍTULO / TITLE:** - Loss of FUBP1 expression in gliomas predicts FUBP1 mutation and is associated with oligodendroglial differentiation, IDH1 mutation and 1p/19q loss of heterozygosity.

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

**REVISTA / JOURNAL:** - Neuropathol Appl Neurobiol. 2013 Oct 3. doi: 10.1111/nan.12088.

●● Enlace al texto completo (gratis o de pago) [1111/nan.12088](#)

**AUTORES / AUTHORS:** - Baumgarten P; Harter PN; Tonjes M; Capper D; Blank AE; Sahm F; von Deimling A; Kolluru V; Schwamb B; Rabenhorst U; Starzetz T; Kogel D; Rieker RJ; Plate KH; Ohgaki H; Radlwimmer B; Zornig M; Mittelbronn M

**INSTITUCIÓN / INSTITUTION:** - Institute of Neurology (Edinger Institute), Goethe University, Frankfurt.

**RESUMEN / SUMMARY:** - AIMS: The Far Upstream Element [FUSE] Binding Protein 1 (FUBP1) regulates target genes, such as the cell cycle regulators MYC and p21. FUBP1 is up-regulated in many tumours and acts as an oncoprotein by stimulating proliferation and inhibiting apoptosis. Recently, FUBP1 mutations were identified in approximately 15% of oligodendrogliomas. To date, all reported FUBP1 mutations have been predicted to inactivate FUBP1, which suggests that in contrast to most other tumours FUBP1 may act as a tumour suppressor in oligodendrogliomas. METHODS: As no data are currently available concerning FUBP1 protein levels in gliomas, we examined the FUBP1 expression profiles of human glial tumours by immunohistochemistry and immunofluorescence. We analysed FUBP1 expression related to morphological differentiation, IDH1 and FUBP1 mutation status, 1p/19q loss of heterozygosity (LOH) as well as proliferation rate. RESULTS: Our findings demonstrate that FUBP1 expression levels are increased in all glioma subtypes as compared to normal central nervous system (CNS) control tissue and are associated with increased proliferation. In contrast, FUBP1 immunonegativity predicted FUBP1 mutation with a sensitivity of 100% and a specificity of 90% in our cohort and was associated with oligodendroglial differentiation, IDH1 mutation and 1p/19q loss of heterozygosity (LOH). Using this approach, we detected a to-date undescribed FUBP1 mutation in an oligodendroglioma. CONCLUSION: In summary, our data indicate an association between of FUBP1 expression and proliferation in gliomas. Furthermore, our findings present FUBP1 immunohistochemical analysis as a helpful additional tool for neuropathological glioma diagnostics predicting FUBP1 mutation.

[504]

**TÍTULO / TITLE:** - Lapatinib alters the malignant phenotype of osteosarcoma cells via downregulation of the activity of the HER2-PI3K/AKT-FASN axis in vitro.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):328-34. doi: 10.3892/or.2013.2825. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2825](#)

**AUTORES / AUTHORS:** - Long XH; Zhang GM; Peng AF; Luo QF; Zhang L; Wen HC; Zhou RP; Gao S; Zhou Y; Liu ZL

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopedics, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, P.R. China.

**RESUMEN / SUMMARY:** - Lapatinib, an inhibitor of human epidermal growth factor receptor 2 (HER2) phosphorylation, has been reported to inhibit several types of tumors such as HER2-overexpressing breast cancer. However, the effect of lapatinib on the malignant phenotype of human osteosarcoma (OS) cells and the potential molecular mechanisms remain unclear. To elucidate the effect of lapatinib on OS, two OS cell lines, U2-OS and MG-63, were utilized in the present study. Various concentrations of lapatinib were used to treat OS cells for different time durations. Cell proliferation was evaluated by MTT and colony formation assays. Flow cytometry (FCM) was used to evaluate cell apoptosis. Wound healing and Transwell invasion assays were performed to examine the migratory and invasive abilities of the cells. To investigate the possible molecular mechanisms involved, the expression of p-HER2, phosphatidylinositol 3-kinase (PI3K), p-AKT, AKT and fatty acid synthase (FASN) protein was detected by western blotting. MTT assays showed that lapatinib inhibited the proliferation of U2-OS and MG-63 cells in a dose- and time-dependent manner, and the rate of colony formation of the lapatinib-treated cells was significantly lower when compared to those cells not treated with lapatinib in both cell lines. FCM assay revealed a significantly higher apoptotic rate in the lapatinib-treated OS cells. Wound healing and Transwell invasion assays revealed that the migratory and invasive abilities of OS cells were significantly inhibited by lapatinib ( $P < 0.05$ ). Western blotting showed that lapatinib suppressed the activity of HER2-PI3K/AKT-FASN in U2-OS and MG-63 cells in vitro. These results suggest that lapatinib may alter the malignant phenotype of OS cells via downregulation of the activity of the HER2-PI3K/AKT-FASN signaling pathway in vitro. Thus, lapatinib may be an effective chemotherapeutic agent for the treatment of osteosarcoma.

[505]

**TÍTULO / TITLE:** - Gene expression profiling for cardiac rejection surveillance is not predictive of post-transplantation skin cancer.

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

**REVISTA / JOURNAL:** - Dermatol Surg. 2013 Oct;39(10):1507-13. doi: 10.1111/dsu.12315.

●● Enlace al texto completo (gratis o de pago) [1111/dsu.12315](http://1111/dsu.12315)

**AUTORES / AUTHORS:** - Hanlon A; O'Neill M; Fang F; Chen H; Lott J; Wigger M; Stasko T

**INSTITUCIÓN / INSTITUTION:** - Yale Dermatologic Surgery, Yale University, New Haven, Connecticut.

**RESUMEN / SUMMARY:** - BACKGROUND: The risk of skin cancer in solid organ transplant recipients (SOTR) is 50 to 100 times as great as in those without a transplant. Multiple factors, including immunosuppression, influence the development of post-transplantation skin cancer. Individuals with cardiac transplant are serially screened for organ rejection and immunosuppressive regimen effectiveness. Gene expression profiling of peripheral blood mononuclear cells has been established as a noninvasive test for monitoring cardiac rejection. OBJECTIVE: We examined individuals with cardiac transplant monitored using peripheral gene expression profiling to determine whether the profile of peripheral blood mononuclear cell activity could correlate with the development of post-transplantation skin cancer. METHODS AND MATERIALS: Sixty-one patient records were examined for initial endomyocardial

biopsy results, gene expression profiling data, immunosuppressive regimens, and post-transplantation skin cancer. RESULTS: There was no relationship between acute rejection and the development of skin cancer. No relationship between peripheral gene expression profiling and the development of post-transplantation skin cancer was observed. The most common skin cancer in the population was squamous cell carcinoma. SOTR suppressed with azathioprine had a significantly higher incidence of squamous cell carcinoma. CONCLUSION: Although gene expression tests have advanced transplant surveillance, they were not associated with post-transplantation skin cancer.

[506]

**TÍTULO / TITLE:** - Mechanisms of apoptosis in irradiated and sunitinib-treated follicular thyroid cancer cells.

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

**REVISTA / JOURNAL:** - Apoptosis. 2013 Nov 9.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0937-0](#)

**AUTORES / AUTHORS:** - Grosse J; Warnke E; Wehland M; Pietsch J; Pohl F; Wise P; Magnusson NE; Eilles C; Grimm D

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, University of Regensburg, Regensburg, Germany.

**RESUMEN / SUMMARY:** - The multikinase inhibitor sunitinib (S) seems to have promising potential in the treatment of thyroid cancer. We focused on the impact of S and/or irradiation (R) on mechanisms of apoptosis in follicular thyroid cancer cells. The effects of R, S and their combination were evaluated 2 and 4 days after treatment, using the human thyroid cancer cell line CGTH W-1. The transcription of genes involved in the regulation of apoptosis was investigated using quantitative real-time PCR. Western blot analyses of caspases and survivin were also performed. S elevated BAX (day 4), CASP9, CASP3, BIRC5 (day 4) and PRKACA (day 4) gene expression, whereas the mRNAs of BCL2, CASP8, PRKCA, ERK1, and ERK2 were not significantly changed. S, R and R+S clearly induced caspase-9 protein and elevated caspase-3 activity. Survivin was down-regulated at day 4 in control cells and the expression was blunted by S treatment. R+S induced survivin expression at day 2 followed by a reduction at day 4 of treatment. Sunitinib and the combined application with radiation induced apoptosis in follicular thyroid cancer cells via the intrinsic pathway of apoptosis. In addition, sunitinib might induce apoptosis via decreased expression of the anti-apoptotic protein survivin. These findings suggest the potential use of sunitinib for the treatment of poorly differentiated follicular thyroid carcinomas.

[507]

**TÍTULO / TITLE:** - Curcumin induces radiosensitivity of in vitro and in vivo cancer models by modulating pre-mRNA processing factor 4 (Prp4).

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

**REVISTA / JOURNAL:** - Chem Biol Interact. 2013 Nov 25;206(2):394-402. doi: 10.1016/j.cbi.2013.10.007. Epub 2013 Oct 19.

●● Enlace al texto completo (gratis o de pago) [1016/j.cbi.2013.10.007](#)

**AUTORES / AUTHORS:** - Shehzad A; Park JW; Lee J; Lee YS

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, College of Natural Sciences, Kyungpook National University, Daegu 702-701, Republic of Korea.

**RESUMEN / SUMMARY:** - Radiation therapy plays a central role in adjuvant strategies for the treatment of both pre- and post-operative human cancers. However, radiation therapy has low efficacy against cancer cells displaying radio-resistant phenotypes. Ionizing radiation has been shown to enhance ROS generation, which mediates apoptotic cell death. Further, concomitant use of sensitizers with radiation improves the efficiency of radiotherapy against a variety of human cancers. Here, the radio-sensitizing effect of curcumin (a derivative of turmeric) was investigated against growth of HCT-15 cells and tumor induction in C57BL/6J mice. Ionizing radiation induced apoptosis through ROS generation and down-regulation of Prp4K, which was further potentiated by curcumin treatment. Flow cytometry revealed a dose-dependent response for radiation-induced cell death, which was remarkably reversed by transfection of cells with Prp4K clone. Over-expression of Prp4K resulted in a significant decrease in ROS production possibly through activation of an anti-oxidant enzyme system. To elucidate an integrated mechanism, Prp4K knockdown by siRNA ultimately restored radiation-induced ROS generation. Furthermore, B16F10 xenografts in C57BL/6J mice were established in order to investigate the radio-sensitizing effect of curcumin in vivo. Curcumin significantly enhanced the efficacy of radiation therapy and reduced tumor growth as compared to control or radiation alone. Collectively, these results suggest a novel mechanism for curcumin-mediated radio-sensitization of cancer based on ROS generation and down-regulation of Prp4K.

[508]

**TÍTULO / TITLE:** - Oridonin Ring A-Based Diverse Constructions of Enone  
Functionality: Identification of Novel Dienone Analogues Effective for Highly Aggressive Breast Cancer by Inducing Apoptosis.

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

**REVISTA / JOURNAL:** - J Med Chem. 2013 Oct 31.

●● [Enlace al texto completo \(gratis o de pago\) 1021/jm401248x](#)

**AUTORES / AUTHORS:** - Ding C; Zhang Y; Chen H; Yang Z; Wild C; Ye N; Ester CD; Xiong A; White MA; Shen Q; Zhou J

**INSTITUCIÓN / INSTITUTION:** - Chemical Biology Program, Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77555, United States.

**RESUMEN / SUMMARY:** - Oridonin (1) has attracted considerable attention in recent years because of its unique and safe anticancer pharmacological profile. Nevertheless, it exhibits moderate to poor effects against highly aggressive cancers including triple-negative and drug-resistant breast cancer cells. Herein, we report the rational design and synthesis of novel dienone derivatives with an additional alpha,beta-unsaturated ketone system diversely installed in the A-ring based on this class of natural scaffold that features dense functionalities and stereochemistry-rich frameworks. Efficient and regioselective enone construction strategies have been established. Meanwhile, a unique 3,7-rearrangement reaction was identified to furnish an unprecedented dienone scaffold. Intriguingly, these new analogues have been demonstrated to significantly induce apoptosis and inhibit colony formation with superior antitumor effects against aggressive and drug-resistant breast cancer cells in

vitro and in vivo while also exhibiting comparable or lower toxicity to normal human mammary epithelial cells in comparison with 1.

[509]

**TÍTULO / TITLE:** - Functional relevance of D,L-sulforaphane-mediated induction of vimentin and plasminogen activator inhibitor-1 in human prostate cancer cells.

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

**REVISTA / JOURNAL:** - Eur J Nutr. 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [1007/s00394-013-0588-5](#)

**AUTORES / AUTHORS:** - Vyas AR; Singh SV

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

**RESUMEN / SUMMARY:** - PURPOSE: D,L-Sulforaphane (SFN) is a promising chemopreventive agent with in vivo efficacy against prostate cancer in experimental rodents. This study was undertaken to determine the role of vimentin and plasminogen activator inhibitor-1 (PAI-1) in anticancer effects of SFN. METHODS: Effect of SFN on levels of different proteins was determined by Western blotting or immunofluorescence microscopy. RNA interference of vimentin and PAI-1 was achieved by transient transfection. Apoptosis was quantified by flow cytometry. Transwell chambers were used to determine cell migration. RESULTS: Exposure of PC-3 and DU145 human prostate cancer cells to SFN resulted in induction of vimentin protein, which was accompanied by down-regulation of E-cadherin protein expression. The SFN-mediated induction of vimentin was also observed in a normal human prostate epithelial cell line. RNA interference of vimentin did not have any appreciable effect on early or late apoptosis resulting from SFN exposure. On the other hand, SFN-mediated inhibition of PC-3 and DU145 cell migration was significantly augmented by knockdown of the vimentin protein. Knockdown of vimentin itself was inhibitory against cell migration. The SFN-treated cells also exhibited induction of PAI-1, which is an endogenous inhibitor of urokinase-type plasminogen activator system. Similar to vimentin, PAI-1 knockdown resulted in a modest augmentation of PC-3 cell migration inhibition by SFN. Tumors from SFN-treated transgenic adenocarcinoma of mouse prostate mice showed a 1.7-fold increase in vimentin protein level compared with control tumors. CONCLUSION: The present study indicates that vimentin and PAI-1 inductions confer modest protection against SFN-mediated inhibition of prostate cancer cell migration.

[510]

**TÍTULO / TITLE:** - Integrative genomic analysis of Temozolomide resistance in Diffuse Large B Cell Lymphoma.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-](#)

[0669](#)

**AUTORES / AUTHORS:** - Leshchenko V; Kuo PY; Jiang Z; Thirukonda VK; Parekh S

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

**RESUMEN / SUMMARY:** - PURPOSE: Despite advances, there is an urgent need for effective therapeutics for relapsed diffuse large B cell lymphoma (DLBCL), particularly in elderly patients and primary CNS lymphoma (PCNSL). Temozolomide (TMZ), an oral DNA alkylating agent routinely used in the therapy of glioblastoma multiforme, is active in PCNSL patients but the response rates are low. The mechanisms contributing to TMZ resistance are unknown. EXPERIMENTAL DESIGN: We undertook an unbiased and genome-wide approach to understand the genomic methylation and gene expression (GE) profiling differences associated with TMZ resistance in DLBCL cell lines and identify mechanisms to overcome TMZ resistance. RESULTS: TMZ was cytotoxic in a subset of DLBCL cell lines, independent of MGMT promoter methylation or protein expression. Using Connectivity mapping (CMAP), we identified several compounds capable of reversing the GE signature associated with TMZ resistance. The demethylating agent Decitabine (DAC) is identified by CMAP as capable of reprogramming GE to overcome TMZ resistance. Treatment with DAC led to increased expression of SMAD1, a transcription factor involved in TGFB/BMP signaling, previously shown to be epigenetically silenced in resistant DLBCL. In vitro and in vivo treatment with a combination of DAC and TMZ had greater anti-lymphoma activity than either drug alone, with complete responses in TMZ resistant DLBCL murine xenograft models. CONCLUSIONS: Integrative genome-wide methylation and GE analysis identified novel genes associated with TMZ resistance and demonstrate potent synergy between DAC and TMZ. The evidence from cell line and murine experiments supports prospective investigation of TMZ in combination with demethylating agents in DLBCL.

[511]

**TÍTULO / TITLE:** - Decreased expression of Small glutamine-rich tetratricopeptide repeat-containing protein (SGT) correlated with prognosis of Hepatocellular carcinoma.

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

**REVISTA / JOURNAL:** - Neoplasma. 2014;61(1):83-9.

**AUTORES / AUTHORS:** - Zhang J; Lu C; He S; Wan C; Zhang Y; Cheng C

**RESUMEN / SUMMARY:** - Small glutamine-rich tetratricopeptide repeat-containing protein (SGT) is an ubiquitously expressed cochaperone of heat shock cognate protein of 70 kDa (Hsc70). SGT binds to the Cterminus of Hsc70 to recruit Hsc70 into complexes of diverse function. SGTB was identified as an isoform of SGT with 60% amino acid sequence homology. To investigate the expression of SGTB in hepatocellular carcinoma (HCC) and determine its correlation with tumor progression and prognosis, we evaluated the expression levels of SGTB in HCCs and corresponding adjacent non-tumor liver tissues. We also assessed the association between their expression and clinicopathologic parameters. The expression of SGTB was absent or low in HCCs while it was notable in paracancerous tissues from 108 patients by western blotting and immunochemistry ( $P < 0.05$ ). Among the 108 HCCs, low expression of SGTB was associated with gender, histological grade ( $P < 0.001$ ) and HBsAg expression ( $P = 0.002$ ). Univariate analysis showed that the low SGTB expression was associated with poor prognosis ( $P < 0.001$ ). Thus, decreased expression of SGTB may be a favorable independent poor prognostic parameter for hepatocellular carcinoma. Keywords: SGTB; Heat stress cognate 70 (Hsc70); HBV; Hepatocellular carcinoma (HCC).

[512]

**TÍTULO / TITLE:** - Venom present in sea anemone (*Heteractis magnifica*) induces apoptosis in non-small-cell lung cancer A549 cells through activation of mitochondria-mediated pathway.

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

**REVISTA / JOURNAL:** - Biotechnol Lett. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1007/s10529-013-1402-4](#)

**AUTORES / AUTHORS:** - Ramezanpour M; da Silva KB; Sanderson BJ

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Biotechnology, School of Medicine, Flinders University of South Australia, Bedford Park, SA, 5042, Australia, [rame0010@flinders.edu.au](mailto:rame0010@flinders.edu.au).

**RESUMEN / SUMMARY:** - Lung cancer is a major cause of cancer deaths throughout the world and the complexity of apoptosis resistance in lung cancer is apparent. Venom from *Heteractis magnifica* caused dose-dependent decreases in survival of the human non-small-cell lung cancer cell line, as determined by the MTT and Crystal Violet assays. The *H. magnifica* venom induced cell cycle arrest and induced apoptosis of A549 cells, as confirmed by annexin V/propidium iodide staining. The venom-induced apoptosis in A549 cells was characterized by cleavage of caspase-3 and a reduction in the mitochondrial membrane potential. Interestingly, crude extracts from *H. magnifica* had less effect on the survival of non-cancer cell lines. In the non-cancer cells, the mechanism via which cell death occurred was through necrosis not apoptosis. These findings are important for future work using *H. magnifica* venom for pharmaceutical development to treat human lung cancer.

[513]

**TÍTULO / TITLE:** - Protein-bound polysaccharide-K augments the anticancer effect of fluoropyrimidine derivatives possibly by lowering dihydropyrimidine dehydrogenase expression in gastrointestinal cancers.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2845-51. doi: 10.3892/or.2013.2788. Epub 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2788](#)

**AUTORES / AUTHORS:** - Mekata E; Murata S; Sonoda H; Shimizu T; Umeda T; Shiomi H; Naka S; Yamamoto H; Abe H; Edamatsu T; Fujieda A; Fujioka M; Wada T; Tani T

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan.

**RESUMEN / SUMMARY:** - Protein-bound polysaccharide-K (PSK) enhances the antitumor effect of anticancer drug when used clinically in combination with such drugs. PSK is known to act by immune-mediated mechanisms; however, the relationship between PSK and metabolic enzymes of anticancer drugs is unknown. We used the collagen gel droplet-embedded culture drug sensitivity test (CD-DST) clinically to evaluate the sensitivity of anticancer drugs. In the present study, we modified the CD-DST by adding peripheral blood mononuclear cells (PBMCs) (immuno-CD-DST) and examined the antitumor effect of PSK in combination with anticancer drugs. First, HCT116 human colon cancer cells were cultured with PSK and 5-fluorouracil (5-FU) or

5'-deoxy-5-fluorouridine (5'-DFUR) in the presence or absence of PBMCs, and the antiproliferative effects were compared. In the presence of PBMCs, PSK augmented the inhibitory effects of 5-FU and 5'-DFUR on HCT116 cell proliferation. Next, using human gastric cancer and colon cancer cell lines, the effects of PSK on mRNA expression of various metabolic enzymes of fluoropyrimidines: dihydropyrimidine dehydrogenase (DPD), thymidylate synthase, thymidine phosphorylase and orotate phosphoribosyl transferase, were examined by real-time PCR. PSK significantly enhanced DPD mRNA expression in all of the cancer cell lines tested, but not those of the other enzymes. Addition of IFN-alpha and TRAIL, cytokines known to inhibit DPD expression, to the cultures reduced DPD mRNA expression in the cancer cells. When PBMC samples collected from healthy volunteers were cultured with PSK, IFN-alpha mRNA expression increased in 3 of the 5 PBMC samples, while TRAIL mRNA expression was unchanged. The present results propose the possibility that PSK induces PBMCs to express IFN-alpha which inhibits DPD expression, and consequently augments the antitumor effect of 5-FU or 5'-DFUR. Immuno-CD-DST is useful for evaluating drugs with immunological mechanisms of action.

[514]

**TÍTULO / TITLE:** - Incidence and prognostic value of multiple gene promoter methylations in gliomas.

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

**REVISTA / JOURNAL:** - J Neurooncol. 2013 Nov 6.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11060-013-1301-5](#)

**AUTORES / AUTHORS:** - Zhang L; Wang M; Wang W; Mo J

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, The First Affiliated Hospital of Xi'an Jiaotong University, College of Medicine, No. 277 Yanta West Road, Xi'an, 710061, Shaanxi, People's Republic of China, [longzhou1983@126.com](mailto:longzhou1983@126.com).

**RESUMEN / SUMMARY:** - Aberrant CpG island methylation is a common phenomenon in malignancy. The methylation status of multiple tumor suppressor genes may serve as a biomarker for early diagnostics and the prediction of prognosis. In this study, we quantitatively determined the promoter methylation status of five tumor-related genes in tumor tissue and paired serum from 240 patients with gliomas. The relationship between hyper-methylation and clinic-pathological parameters was evaluated, and the prognostic value of the methylation status was determined. Hypermethylation in serum was shown to be accompanied by hypermethylation in paired tumor tissues. In both tumors and serum, methylation of polymerase-1 (PARP-1), SHP-1, DAPK-1 and TIMP-3 genes was at significantly higher levels in high-grade compared with low-grade gliomas, indicating that the promoter methylation status positively correlates with tumor grade. In malignant gliomas, the serum methylation levels of PARP-1, and SHP-1 together with IDH-1 mutations were found to be independent prognostic factors for overall survival. Moreover, hypermethylation of PARP-1 in serum correlated with a shorter progression-free survival time. These results suggest that hypermethylation in gliomas correlates with increased malignancy and poor prognosis. Analysis of the serum promoter methylation status of multiple genes could therefore be used as a biomarker for the detection and evaluation of the prognosis of glioma patients.

[515]

**TÍTULO / TITLE:** - Anti-apoptotic effect of clusterin on cisplatin-induced cell death of retinoblastoma cells.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2713-8. doi: 10.3892/or.2013.2764. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2764](#)

**AUTORES / AUTHORS:** - Song HB; Jun HO; Kim JH; Yu YS; Kim KW; Min BH; Kim JH

**INSTITUCIÓN / INSTITUTION:** - Fight against Angiogenesis-Related Blindness Laboratory, Clinical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea.

**RESUMEN / SUMMARY:** - Clusterin is a cytoprotective chaperone protein that is known to protect various retinal cells. It was also reported to be overexpressed in several types of malignant tumors, whose chemoresistance correlates with the expression of clusterin. Herein, we investigated the effect of clusterin on cisplatin-induced cell death of retinoblastoma cells. Firstly, evaluation of clusterin expression demonstrated that it was highly expressed in human retinoblastoma tissues and cell lines (SNUOT-Rb1 and Y79) particularly in the area between viable cells around vessels and necrotic zones in the relatively avascular area in human retinoblastoma tissues. Furthermore, the effects of cisplatin on retinoblastoma cells were evaluated. Cisplatin (1 microg/ml) significantly affected cell viability of SNUOT-Rb1 cells by inducing caspase-3-dependent apoptosis. Notably, the cell death due to cisplatin was prevented by 5 microg/ml of clusterin administered 4 h prior to cisplatin treatment by inhibiting cisplatin-induced apoptosis. Furthermore, overexpression of clusterin exerted its anti-apoptotic effect on cisplatin-induced apoptosis, and effectively prevented cisplatin-induced cell death. These data suggest that clusterin, found to be expressed in human retinoblastoma, may exert anti-apoptotic effects on cisplatin-induced apoptosis and prevent cell death. Therefore, clusterin can contribute to cisplatin resistance of retinoblastoma.

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[516]

**TÍTULO / TITLE:** - Synergistic anti-leukemic activity of imatinib in combination with a small molecule Grb2 SH2 domain binding antagonist.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Oct 31. doi: 10.1038/leu.2013.323.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.323](#)

**AUTORES / AUTHORS:** - Zhang M; Luo Z; Liu H; Croce CM; Burke TR Jr; Bottaro DP

**INSTITUCIÓN / INSTITUTION:** - The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA.

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[517]

**TÍTULO / TITLE:** - Alternative Therapeutic Approach to Renal Cell Carcinoma: Induction of Apoptosis with Combination of Vitamin K3 and D-fraction.

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

**REVISTA / JOURNAL:** - J Endourol. 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1089/END-2013-0207.ECB.R1](#)

**AUTORES / AUTHORS:** - Degen M; Alexander B; Choudhury M; Eshghi M; Konno S  
**INSTITUCIÓN / INSTITUTION:** - New York Medical College, Urology, Tarrytown, New York, United States ; [michael.degen@me.com](mailto:michael.degen@me.com).

**RESUMEN / SUMMARY:** - Abstract Purpose: Due to a dismal prognosis for advanced renal cell carcinoma (RCC), an alternative therapeutic approach, using vitamin K3 (VK3) and D-fraction (DF) was investigated. VK3 is a synthetic VK derivative and DF is a bioactive mushroom extract, and they have been shown to have antitumor activity. We examined if the combination of VK3 and DF would exhibit the improved anticancer effect on RCC in vitro. Materials and Methods: Human RCC, ACHN cell line, were treated with varying concentrations of VK3, DF, or a combination of the two. Cell viability was assessed at 72 hours by MTT assay. To explore the possible anticancer mechanism, studies on cell cycle, chromatin modifications, and apoptosis were conducted. Results: VK3 alone led to a ~20% reduction in cell viability at 4 microM, while DF alone induced a 20-45% viability reduction at  $\geq 500$  microg/mL. However, combination of VK3 (4 microM) and DF (300 microg/mL) led to a drastic  $>90\%$  viability reduction. Cell cycle analysis indicated that VK3/DF treatment induced a G1 cell cycle arrest, accompanied by the up-regulation of p21WAF1 and p27Kip1. Histone deacetylase (HDAC) was also significantly (.60%) inactivated, indicating chromatin modifications. In addition, Western blot analysis revealed that the up-regulation of Bax and activation of poly-(ADP-ribose)-polymerase (PARP) were seen in VK3/DF-treated cells, indicating induction of apoptosis. Conclusions: The combination of VK3 and DF can lead to a profound reduction in ACHN cell viability, through a p21WAF1-mediated G1 cell cycle arrest, and ultimately induces apoptosis. Therefore, the combination of VK3/DF may have clinical implications as an alternative, improved therapeutic modality for advanced RCC.

[518]

**TÍTULO / TITLE:** - Lantabetulic Acid Derivatives Induce G1 Arrest and Apoptosis in Human Prostate Cancer Cells.

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

**REVISTA / JOURNAL:** - Arch Pharm (Weinheim). 2013 Nov 18. doi: 10.1002/ardp.201300224.

●● Enlace al texto completo (gratis o de pago) [1002/ardp.201300224](https://doi.org/10.1002/ardp.201300224)

**AUTORES / AUTHORS:** - Lin KW; Lin ZY; Huang AM; Weng JR; Yen MH; Yang SC; Lin CN

**INSTITUCIÓN / INSTITUTION:** - Faculty of Fragrance and Cosmetics, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan.

**RESUMEN / SUMMARY:** - Ten new lantabetulic acid (1) derivatives 2-11 were synthesized and their cytotoxicities against human prostate cancer cells were evaluated. PC3 cells treated with 10  $\mu$ M 8 exhibited the most potent G1 phase arrest. In addition, 10  $\mu$ M 8 markedly decreased the levels of cyclin E and cdk2 and caused an increase in the p21 and p27 levels, while 20  $\mu$ M 8 mainly led to cell death through the apoptotic pathway, which correlated with an increase in reactive oxygen species levels, decreased expression levels of Bcl-2 and caspase-8, the induction of mitochondrial changes, and decreased levels of cytochrome c in mitochondria. The dual action of 8 could provide a new approach for the development of chemotherapeutic drugs.

[519]

**TÍTULO / TITLE:** - Clinical Significance of Erlotinib Monotherapy for Gefitinib-resistant Non-small Cell Lung Cancer with EGFR Mutations.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):5083-9.

**AUTORES / AUTHORS:** - Koyama N; Uchida Y

**INSTITUCIÓN / INSTITUTION:** - Division of Pulmonary Medicine, Clinical Department of Internal Medicine, Jichi Medical University Saitama Medical Center, 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama, 330-8503, Japan. [nkoyama@jichi.ac.jp](mailto:nkoyama@jichi.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: The efficacy of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib is difficult to be accurately assessed in patients with non-small cell lung cancer (NSCLC) because it is commonly employed after failure of another EGFR-TKI, gefitinib. PATIENTS AND METHODS: Medical records from 104 patients with NSCLC treated with erlotinib were retrospectively reviewed. RESULTS: There were no significant differences in erlotinib efficacy between EGFR-mutated NSCLC with gefitinib resistance and NSCLC with wild-type EGFR. A therapeutic response of disease control (DC) and the onset of skin rash prolonged the progression-free survival (PFS), whereas the onset of interstitial lung disease shortened both PFS and overall survival (OS). The DC group also experienced prolonged OS. CONCLUSION: Erlotinib may be a therapeutic option for EGFR-mutated NSCLC with gefitinib resistance, as well as for NSCLC with wild-type EGFR. Therapeutic response of DC and the onset of the described adverse events may be practical predictors of survival in erlotinib treatment.

[520]

**TÍTULO / TITLE:** - Blocking autophagy enhances the apoptosis effect of bufalin on human hepatocellular carcinoma cells through endoplasmic reticulum stress and JNK activation.

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

**REVISTA / JOURNAL:** - Apoptosis. 2013 Oct 10.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10495-013-0914-7](#)

**AUTORES / AUTHORS:** - Hu F; Han J; Zhai B; Ming X; Zhuang L; Liu Y; Pan S; Liu T

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, 150001, China.

**RESUMEN / SUMMARY:** - Bufalin extracts are a part of traditional Chinese medicine, Chansu. In the current study, we investigated the effect of bufalin on the proliferation of the human hepatocellular carcinoma (HCC) cell lines, Huh-7 and HepG-2, and explored the therapeutic potential of the drug. Our results demonstrated that bufalin markedly inhibited cell proliferation and promoted apoptosis in the Huh-7 and HepG-2 cells in vitro. The underlying mechanism of the bufalin-induced apoptosis was the induction of endoplasmic reticulum (ER) stress via the IRE1-JNK pathway. In addition, during the ER stress response, the autophagy pathway, characterized by the conversion of LC3-I to LC3-II, was activated, resulting in increased Beclin-1 protein levels, decreased p62 expression and stimulation of autophagic flux. Our data supported the pro-survival role of bufalin-induced autophagy when the autophagy

pathway was blocked with specific chemical inhibitors; the involvement of the IRE1 pathway in the ER stress-induced autophagy was also demonstrated when the expression of IRE1 and CHOP was silenced using siRNA. These data indicate that combining bufalin with a specific autophagy inhibitor could be a promising therapeutic approach for the treatment of HCC.

[521]

**TÍTULO / TITLE:** - Multiple regression analysis of factors predicting mycophenolic Acid free fraction in 91 adult organ transplant recipients.

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

**REVISTA / JOURNAL:** - Ther Drug Monit. 2013 Dec;35(6):867-71. doi: 10.1097/FTD.0b013e318299fa38.

●● [Enlace al texto completo \(gratis o de pago\) 1097/FTD.0b013e318299fa38](#)

**AUTORES / AUTHORS:** - Kiang TK; Ng K; Ensom MH

**INSTITUCIÓN / INSTITUTION:** - \*Faculty of Pharmaceutical Sciences, The University of British Columbia; daggerChild and Family Research Institute; and double daggerDepartment of Pharmacy, Children's & Women's Health Centre of British Columbia, Vancouver, British Columbia, Canada.

**RESUMEN / SUMMARY:** - BACKGROUND: Mycophenolic acid (MPA) is an antirejection drug used in various types of solid organ transplants. MPA is extensively bound to albumin, and free MPA is thought to be the primary immunosuppressive agent. Little is known of what contributes to the wide interindividual variability in the observed MPA free fraction (MPAf) in humans. The purpose of this study was to determine, using multiple regression analysis of demographic and laboratory variables that are routinely collected during clinic visits, patient factors that predict MPAf in a large sample (n = 91) of organ transplant recipients. METHODS: Age, weight, height, total daily MPA dose, albumin, serum creatinine (SrCr), and MPAf were obtained from islet (n = 16), kidney (n = 28), and heart/lung (n = 47) transplant recipients. Multiple linear regression analysis and the Spearman rank correlation were conducted using SigmaStat (version 3.5 for Windows). Significance was set a priori at P = 0.05. RESULTS: The pooled data can be described as (mean +/- SD) follows: age (52 +/- 13 years), weight (72 +/- 15 kg), height (169 +/- 9 cm), total daily MPA dose (1632 +/- 667 mg), albumin (42 +/- 7 g/L), SrCr (112 +/- 34 micromol/L), and MPAf (2.9% +/- 3.5%). Multiple regression of all commonly acquired variables generated the following equation:  $MPAf = 1.865 + (0.0357 \times \text{age (yrs)}) + (0.0125 \times \text{weight (kg)}) - (0.0202 \times \text{height (cm)}) - (0.000323 \times \text{total daily dose (mg)}) + (0.0122 \times \text{albumin (g/L)}) + (0.0160 \times \text{SrCr (micromol/L)})$  (r = 0.06), but none of the variables were significant predictors of MPAf (P > 0.05). The Spearman rank correlation of each individual variable confirmed lack of significant correlation with MPAf. CONCLUSIONS: To our knowledge, this is the first study attempting to describe factors predicting MPAf in adult organ transplant recipients involving a large sample size. The novel findings of lack of significant predictors warrant further investigations using additional patient factors.

[522]

**TÍTULO / TITLE:** - Cyclin-dependent kinase 1 inhibitor RO3306 promotes mitotic slippage in paclitaxel-treated HepG2 cells.

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

**REVISTA / JOURNAL:** - Neoplasma. 2014;61(1):41-7.

**AUTORES / AUTHORS:** - Xiao J; Qiu P; Lai X; He P; Wu Y; Du B; Tan Y

**RESUMEN / SUMMARY:** - Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm and current systemic chemotherapy are mostly ineffective. Paclitaxel (PTX) has acclinically significant effect on many malignant tumors. Cells treated with PTX undergo reversible mitotic arrest and although high doses can cause side effects it may also induce apoptosis. We investigated the effect of asequential combination of PTX and RO3306, acyclin-dependent kinase 1 inhibitor, on the hepatocellular carcinoma HepG2 cell line. The sequential drug treatment protocol involved the addition of PTX (0.2 micromol/L) for 18 h followed by RO3306 (2 micromol/L) for a further 6 h. Cell viability and proliferation were measured using tetrazolium dye (MTT) and colony formation assay. Cell cycle profiles were established by flow cytometry. The expression level of protein was examined by immunoblotting. We observed asynergistic effect of PTX and RO3306 treatment on cell growth and proliferation as well as an increased proportion of cells in sub-G1 phase. Expression levels of cyclin B, cyclin E and phosphorylated Histone H3 demonstrated that RO3306 enhanced apoptosis in PTX treated cells by mitotic slippage. Our data suggested that the combination of PTX and RO3306 may be an effective therapeutic combination for the treatment of liver cancer. Keywords: paclitaxel; RO3306; apoptosis; mitotic slippage; HepG2 cells.

[523]

**TÍTULO / TITLE:** - The effect of Amaryllidaceae alkaloids haemanthamine and haemanthidine on cell cycle progression and apoptosis in p53-negative human leukemic Jurkat cells.

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

**REVISTA / JOURNAL:** - Phytomedicine. 2013 Oct 29. pii: S0944-7113(13)00362-0. doi: 10.1016/j.phymed.2013.09.005.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.phymed.2013.09.005](#)

**AUTORES / AUTHORS:** - Havelek R; Seifrtova M; Kralovec K; Bruckova L; Cahlikova L; Dalecka M; Vavrova J; Rezacova M; Opletal L; Bilkova Z

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**RESUMEN / SUMMARY:** - Plants from the Amaryllidaceae family have been shown to be a promising source of biologically active natural compounds of which some selected are currently in pre-clinical development. Regardless of interesting pioneer works, little is known about Amaryllidaceae alkaloids that have shown promising anti-cancer activities. The crinane group of the Amaryllidaceae, including haemanthamine and haemanthidine, was amongst the first of these compounds to exhibit an interesting cytotoxic potential against cancer cell lines. However, the mechanism of cytotoxic and anti-proliferative activity is not yet entirely clear. The primary objectives of the current study were to investigate the effects of haemanthamine and haemanthidine on the induction of apoptosis and the cell cycle regulatory pathway in p53-null Jurkat cells. Results indicate that haemanthamine and haemanthidine treatment decreases cell viability and mitochondrial membrane potential, leads to a decline in the percentage of

cells in the S phase of the cell cycle, induces apoptosis detected by Annexin V staining and increases caspase activity. Dose dependent apoptosis was cross verified by fluorescence and bright field microscopy through Annexin V/propidium iodine staining and morphological changes which characteristically attend programmed cell death. The apoptotic effect of haemanthamine and haemanthidine on leukemia cells is more pronounced than that of gamma radiation. Contrary to gamma radiation, Jurkat cells do not completely halt the cell cycle 24h upon haemanthamine and haemanthidine exposure. Both Amaryllidaceae alkaloids accumulate cells preferentially at G1 and G2 stages of the cell cycle with increased p16 expression and Chk1 Ser345 phosphorylation. Concerning the pro-apoptotic effect, haemanthidine was more active than haemanthamine in the Jurkat leukemia cell line.

[524]

**TÍTULO / TITLE:** - Folic acid-coupled nano-paclitaxel liposome reverses drug resistance in SKOV3/TAX ovarian cancer cells.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Nov 25.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1097/CAD.0000000000000047](#)

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**RESUMEN / SUMMARY:** - Chemotherapy could be used as an effective treatment for ovarian cancer and subsequent peritoneal metastasis. Administration of chemoagents in a targeted manner may bring the advantage of higher efficiency and lower drug resistance. In the present study, folate receptor (FR)-targeted nano-paclitaxel formulations were generated and tested for cytotoxicity in a peritoneal xenograft model of paclitaxel-resistant ovarian cancer and SKOV3/TAX cell lines. Immunocytochemical staining confirmed the expression of FR in both SKOV3 and SKOV3/TAX cells. The enrichment of the folic acid-coupled PEGylated nano-paclitaxel liposome (FA-NP) in FR-positive cells was visualized with fluorescence. The uptake of the FA-NP peaked at 4 h and was more robust than nontargeted PEGylated nano-paclitaxel liposome (NP). FA-NP but not NP markedly inhibited the growth of ovarian cancer cells and induced a two-fold increase in the doubling time. The cytotoxic effects of FA-NP were more potent than NP in both SKOV3 cells [50% of inhibition concentration (IC<sub>50</sub>), 5.67 vs. 50.2 mug/ml, FA-NP vs. NP] and SKOV3/TAX cells (IC<sub>50</sub>, 0.38 vs. >200 mug/ml, FA-NP vs. NP). FA-NP caused more G2-M cell cycle arrest and apoptotic changes in ovarian cancer cells than NP or regular paclitaxel. However, these effects were blunted in the presence of free FA, which competitively inhibited the receptor-mediated uptake of FA-NP particles. Intraperitoneal (i.p.) administration of FA-NP but not regular paclitaxel, NP, or vehicle significantly prolonged the survival and reduced tumor nodule number (2.9+/-0.3) in BALB/c nude mice. FA-NP also markedly enhanced the percentage of apoptotic cells in peritoneal xenografts of paclitaxel-resistant ovarian cancer cells (44.6+/-8.5 vs. 3.2+/-1.1% for vehicle, 22.4+/-5.9% for regular paclitaxel, and 35.2+/-7.7% for NP; P<0.05). However, intravenous administration of FA-NP at the same dose failed to induce apoptosis (20.1+/-6.2%; P<0.05) and inhibit tumor nodule

number to the same extent as intraperitoneal administration. FA-NP reversed the drug resistance in paclitaxel-resistant SKOV3/TAX ovarian cancer cells both in vitro and in vivo. Localized and targeted administration of the FR-targeted chemoagents might prolong the survival time in patients with drug-resistant ovarian cancer.

[525]

**TÍTULO / TITLE:** - Astrocyte elevated gene-1: a novel independent prognostic biomarker for metastatic ovarian tumors.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 16.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1400-0](#)

**AUTORES / AUTHORS:** - Li C; Chen K; Cai J; Shi QT; Li Y; Li L; Song H; Qiu H; Qin Y; Geng JS

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, The Third Affiliated (Tumour) Hospital, Harbin Medical University, Harbin, 150040, China.

**RESUMEN / SUMMARY:** - Astrocyte elevated gene-1 (AEG-1), a novel tumor-associated gene, was found overexpressed in many tumors. Therefore, our purpose is to estimate whether AEG-1 overexpression is a novel predictor of prognostic marker in metastatic ovarian tumors. Immunohistochemistry was used to estimate AEG-1 overexpression in metastatic ovarian tumors from 102 samples. The association between AEG-1 expression and prognosis was estimated by univariate and multivariate survival analyses with Cox regression. The log-rank test was used to identify any differences in the prognosis between the two groups. The median overall and progression-free survival rates of patients with tumors from gastrointestinal tract origin were 0.97 and 0.51 years, respectively. Similarly, survival rates of patients with tumors of breast origin were 2.68 and 1.96 years ( $P < 0.0001$ ). Of 102 patients, 77 had high expression, and AEG-1 overexpression had a significant link of prognosis in metastatic ovarian patients ( $P < 0.01$ ). On the other hand, medians of overall survival and progression-free survival of patients with tumors of gastrointestinal tract origin were significantly lower than those of patients with tumors of breast origin ( $P < 0.0001$ ). Patients with metastatic ovarian tumors of breast origin had significantly better prognosis than those with the tumors from gastrointestinal tract primary malignancies. It is suggested that AEG-1 overexpression might be an independent prognostic marker of metastatic ovarian tumors.

[526]

**TÍTULO / TITLE:** - Events associated with apoptotic effect of p-Coumaric acid in HCT-15 colon cancer cells.

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

**REVISTA / JOURNAL:** - World J Gastroenterol. 2013 Nov 21;19(43):7726-34. doi: 10.3748/wjg.v19.i43.7726.

●● Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i43.7726](#)

**AUTORES / AUTHORS:** - Jaganathan SK; Supriyanto E; Mandal M

**INSTITUCIÓN / INSTITUTION:** - Saravana Kumar Jaganathan, Eko Supriyanto, IJ N-UTM Cardiovascular Engineering Centre, Faculty of Bioscience and Medical Engineering, Universiti Teknologi Malaysia, Johor Bahru 81310, Malaysia.

**RESUMEN / SUMMARY:** - AIM: To investigate the events associated with the apoptotic effect of p-Coumaric acid, one of the phenolic components of honey, in human colorectal carcinoma (HCT-15) cells. METHODS: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tertrazolium-bromide assay was performed to determine the antiproliferative effect of p-Coumaric acid against colon cancer cells. Colony forming assay was conducted to quantify the colony inhibition in HCT 15 and HT 29 colon cancer cells after p-Coumaric acid treatment. Propidium Iodide staining of the HCT 15 cells using flow cytometry was done to study the changes in the cell cycle of treated cells. Identification of apoptosis was done using scanning electron microscope and photomicrograph evaluation of HCT 15 cells after exposing to p-Coumaric acid. Levels of reactive oxygen species (ROS) of HCT 15 cells exposed to p-Coumaric acid was evaluated using 2', 7'-dichlorofluorescein-diacetate. Mitochondrial membrane potential of HCT-15 was assessed using rhodamine-123 with the help of flow cytometry. Lipid layer breaks associated with p-Coumaric acid treatment was quantified using the dye merocyanine 540. Apoptosis was confirmed and quantified using flow cytometric analysis of HCT 15 cells subjected to p-Coumaric acid treatment after staining with YO-PRO-1. RESULTS: Antiproliferative test showed p-Coumaric acid has an inhibitory effect on HCT 15 and HT 29 cells with an IC<sub>50</sub> (concentration for 50% inhibition) value of 1400 and 1600 μmol/L respectively. Colony forming assay revealed the time-dependent inhibition of HCT 15 and HT 29 cells subjected to p-Coumaric acid treatment. Propidium iodide staining of treated HCT 15 cells showed increasing accumulation of apoptotic cells (37.45 +/- 1.98 vs 1.07 +/- 1.01) at sub-G1 phase of the cell cycle after p-Coumaric acid treatment. HCT-15 cells observed with photomicrograph and scanning electron microscope showed the signs of apoptosis like blebbing and shrinkage after p-Coumaric acid exposure. Evaluation of the lipid layer showed increasing lipid layer breaks was associated with the growth inhibition of p-Coumaric acid. A fall in mitochondrial membrane potential and increasing ROS generation was observed in the p-Coumaric acid treated cells. Further apoptosis evaluated by YO-PRO-1 staining also showed the time-dependent increase of apoptotic cells after treatment. CONCLUSION: These results depicted that p-Coumaric acid inhibited the growth of colon cancer cells by inducing apoptosis through ROS-mitochondrial pathway.

[527]

**TÍTULO / TITLE:** - Ursolic acid inhibits the growth of colon cancer-initiating cells by targeting STAT3.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4279-84.

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**RESUMEN / SUMMARY:** - BACKGROUND: We have previously reported Signal Transducer and Activator of Transcription 3 (STAT3) to be constitutively activated in aldehyde dehydrogenase (ALDH)(+)/cluster of differentiation-133 (CD133)(+) colon cancer-initiating cells. In the present study we tested the efficacy of inhibiting STAT3 signaling in human colon cancer-initiating cells by ursolic acid (UA), which exists

widely in fruits and herbs. RESULTS: Our data demonstrated that UA inhibited STAT3 phosphorylation, and induced caspase-3 cleavage of ALDH(+)/CD133(+) colon cancer-initiating cells. UA also reduced cell viability and inhibited tumor sphere formation of colon cancer-initiating cells, more potently than two other natural compounds, resveratrol and capsaicin. UA also inhibited the activation of STAT3 induced by interleukin-6 in DLD-1 colon cancer cells. Furthermore, daily administration of UA suppressed HCT116 tumor growth in mice in vivo. CONCLUSION: Our results suggest STAT3 to be a target for colon cancer prevention. UA, a dietary agent, might offer an effective approach for colorectal carcinoma prevention by inhibiting persistently activated STAT3 in cancer stem cells.

[528]

**TÍTULO / TITLE:** - Refinement of the prediction of N-acetyltransferase 2 (NAT2) phenotypes with respect to enzyme activity and urinary bladder cancer risk.

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

**REVISTA / JOURNAL:** - Arch Toxicol. 2013 Dec;87(12):2129-39. doi: 10.1007/s00204-013-1157-7. Epub 2013 Nov 13.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00204-013-1157-7](#)

**AUTORES / AUTHORS:** - Selinski S; Blaszkewicz M; Ickstadt K; Hengstler JG; Golka K

**INSTITUCIÓN / INSTITUTION:** - Leibniz Research Centre for Working Environment and Human Factors (IfAdo), Ardeystrasse 67, 44139, Dortmund, Germany, [selinski@ifado.de](mailto:selinski@ifado.de).

**RESUMEN / SUMMARY:** - Polymorphisms of N-acetyltransferase 2 (NAT2) are well known to modify urinary bladder cancer risk as well as efficacy and toxicity of pharmaceuticals via reduction in the enzyme's acetylation capacity. Nevertheless, the discussion about optimal NAT2 phenotype prediction, particularly differentiation between different degrees of slow acetylation, is still controversial. Therefore, we investigated the impact of single nucleotide polymorphisms and their haplotypes on slow acetylation in vivo and on bladder cancer risk. For this purpose, we used a study cohort of 1,712 bladder cancer cases and 2,020 controls genotyped for NAT2 by RFLP-PCR and for the tagSNP rs1495741 by TaqMan(®) assay. A subgroup of 344 individuals was phenotyped by the caffeine test in vivo. We identified an 'ultra-slow' acetylator phenotype based on combined \*6A/\*6A, \*6A/\*7B and \*7B/\*7B genotypes containing the homozygous minor alleles of C282T (rs1041983, \*6A, \*7B) and G590A (rs1799930, \*6A). 'Ultra-slow' acetylators have significantly about 32 and 46 % lower activities of caffeine metabolism compared with other slow acetylators and with the \*5B/\*5B genotypes, respectively (P < 0.01, both). The 'ultra-slow' genotype showed an association with bladder cancer risk in the univariate analysis (OR = 1.31, P = 0.012) and a trend adjusted for age, gender and smoking habits (OR = 1.22, P = 0.082). In contrast, slow acetylators in general were not associated with bladder cancer risk, neither in the univariate (OR = 1.02, P = 0.78) nor in the adjusted (OR = 0.98, P = 0.77) analysis. In conclusion, this study suggests that NAT2 phenotype prediction should be refined by consideration of an 'ultra-slow' acetylation genotype.

[529]

**TÍTULO / TITLE:** - Expression of nucleoside metabolizing enzymes in myelodysplastic syndromes and modulation of response to azacitidine.

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

**REVISTA / JOURNAL:** - Leukemia. 2013 Nov 6. doi: 10.1038/leu.2013.330.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.330](#)

**AUTORES / AUTHORS:** - Valencia A; Masala E; Rossi A; Martino A; Sanna A; Buchi F; Canzian F; Cilloni D; Gaidano V; Voso MT; Kosmider O; Fontenay M; Gozzini A; Bosi A; Santini V

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Università degli Studi di Firenze, AOU Careggi. Florence, Italy.

**RESUMEN / SUMMARY:** - The nucleoside analog azacitidine (AZA) is used in the treatment of myelodysplastic syndromes (MDS), but 30-40% of patients fail to respond or relapse after treatment. Hence, to identify new molecular alterations that allow for identification of patients unlikely to respond to AZA could impact the utility of this therapy. We determined expression levels of genes involved in AZA metabolism: UCK1, UCK2, DCK, hENT1, RRM1, and RRM2 using quantitative PCR in samples from 57 patients with MDS who received AZA. Lower expression of UCK1 was seen in patients without a response to AZA (median 0.2 vs 0.49 for patients with response to AZA, P=0.07). This difference in UCK1 expression was not influenced by aberrant methylation of the UCK1 promoter. In addition, the seven polymorphic loci found in the coding sequence were not associated with UCK1 gene expression nor AZA response. Silencing of UCK1 by siRNA leads to blunted response to AZA in vitro. The univariate analysis revealed that patients expressing lower than median levels of UCK1 had a shorter overall survival (P=0.049). Our results suggest that expression level of UCK1 is correlated with clinical outcome and may influence the clinical response to AZA treatment in patients with MDS. Leukemia accepted article preview online, 6 November 2013; doi:10.1038/leu.2013.330.

[530]

**TÍTULO / TITLE:** - Serpin B5 is a CEA-interacting biomarker for colorectal cancer.

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

**REVISTA / JOURNAL:** - Int J Cancer. 2013 Sep 30. doi: 10.1002/ijc.28494.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28494](#)

**AUTORES / AUTHORS:** - Baek JY; Yeo HY; Chang HJ; Kim KH; Kim SY; Park JW; Park SC; Choi HS; Kim DY; Oh JH

**INSTITUCIÓN / INSTITUTION:** - Center for Colorectal Cancer, National Cancer Center, Goyang, Republic of Korea.

**RESUMEN / SUMMARY:** - Serpin B5 is a candidate tumour suppressor, but its oncogenic activity has also been reported. Its function may be affected by protein interactions. The aim of this study was to assess the relationship between serpin B5 and carcinoembryonic antigen (CEA) expression in colorectal cancer (CRC). We also analysed the clinicopathological significance of serpin B5 expression in patients with CRC. Downregulation of serpin B5 was identified in a CEA-suppressed LoVo cell line using two-dimensional gel electrophoresis (2-DE) and matrix-associated laser desorption ionisation-mass spectrometry (MALDI-MS). The specific interaction and co-localisation of serpin B5 with CEA were confirmed by co-immunoprecipitation and confocal microscopy. Western blot analysis and ELISAs revealed significant positive

correlations between levels of serpin B5 and CEA in human colon cancer cell lines and in the blood of patients with CRC. Tissue expression of serpin B5 in 377 patients with CRC was significantly associated with serum CEA, histological grade, stage, lymph node metastasis, lymphatic and perineural invasion, and infiltrative border. Strong expression of serpin B5 was also associated with a reduced DFS ( $p = 0.001$ ) and OS ( $p = 0.017$ ). Together, these findings describe a relationship between serpin B5 and CEA expression in CRC. Strong expression of serpin B5 was associated with a worse prognosis in patients with CRC and its expression may correlate with CEA levels in CRC.

[531]

**TÍTULO / TITLE:** - Establishment of new intraperitoneal paclitaxel-resistant gastric cancer cell lines and comprehensive gene expression analysis.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4299-307.

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**RESUMEN / SUMMARY:** - BACKGROUND: Intraperitoneal (i.p.) chemotherapy with paclitaxel is a potential therapeutic modality for patients with peritoneal metastasis of gastric cancer. To overcome paclitaxel resistance, which is a major clinical problem with this modality, prediction of i.p. paclitaxel resistance is critically important. MATERIALS AND METHODS: We developed three new i.p. paclitaxel-resistant cell lines from parental gastric cancer cell lines by an in vivo selection method using i.p. paclitaxel chemotherapy. With these cell lines, we performed gene expression profiling analysis to select up-regulated genes in i.p. paclitaxel-resistant cells and validated the genes with clinical samples. RESULTS: We successfully isolated nine up-regulated genes in i.p. paclitaxel-resistant cell lines compared with parental cells by microarray analysis, followed by confirmation with quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR). Among these, we identified four genes, namely kinesin family member-23 (KIF23), ERBB2 interacting protein (ERBB2IP), ATPase family, AAA domain containing-2 (ATAD2) and PHD finger protein (PHF19) as candidate genes for paclitaxel resistance after validation with clinical samples derived from responders and non-responders to paclitaxel treatment. CONCLUSION: These i.p. paclitaxel-resistant cell lines are ideal models for understanding the mechanism of resistance to i.p. paclitaxel and development of a new therapeutic modality. Four up-regulated genes may be potential new predictive markers for resistance to i.p. paclitaxel in patients with peritoneal metastasis of gastric cancer.

[532]

**TÍTULO / TITLE:** - Identification of biomarkers for apoptosis in cancer cell lines using metabolomics: tools for individualized medicine.

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

**REVISTA / JOURNAL:** - J Intern Med. 2013 Nov;274(5):425-39. doi: 10.1111/joim.12117.

●● Enlace al texto completo (gratis o de pago) [1111/joim.12117](http://1111/joim.12117)

**AUTORES / AUTHORS:** - Halama A; Riesen N; Moller G; Hrabe de Angelis M; Adamski J

**INSTITUCIÓN / INSTITUTION:** - Helmholtz Zentrum Munchen, German Research Center for Environmental Health, Institute of Experimental Genetics, Genome Analysis Center, Neuherberg, Germany.

**RESUMEN / SUMMARY:** - BACKGROUND: Metabolomics is a versatile unbiased method to search for biomarkers of human disease. In particular, one approach in cancer therapy is to promote apoptosis in tumour cells; this could be improved with specific biomarkers of apoptosis for monitoring treatment. We recently observed specific metabolic patterns in apoptotic cell lines; however, in that study, apoptosis was only induced with one pro-apoptotic agent, staurosporine. OBJECTIVE: The aim of this study was to find novel biomarkers of apoptosis by verifying our previous findings using two further pro-apoptotic agents, 5-fluorouracil and etoposide, that are commonly used in anticancer treatment. METHODS: Metabolic parameters were assessed in HepG2 and HEK293 cells using the newborn screening assay adapted for cell culture approaches, quantifying the levels of amino acids and acylcarnitines with mass spectrometry. RESULTS: We were able to identify apoptosis-specific changes in the metabolite profile. Moreover, the amino acids alanine and glutamate were both significantly up-regulated in apoptotic HepG2 and HEK293 cells irrespective of the apoptosis inducer. CONCLUSION: Our observations clearly indicate the potential of metabolomics in detecting metabolic biomarkers applicable in theranostics and for monitoring drug efficacy.

[533]

**TÍTULO / TITLE:** - Increased C-reactive protein implies a poorer stage-specific prognosis in colon cancer.

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

**REVISTA / JOURNAL:** - Acta Oncol. 2013 Nov;52(8):1691-8. doi: 10.3109/0284186X.2013.835494.

●● Enlace al texto completo (gratis o de pago) [3109/0284186X.2013.835494](http://3109/0284186X.2013.835494)

**AUTORES / AUTHORS:** - Kersten C; Louhimo J; Algars A; Lahdesmaki A; Cvancerova M; Stenstedt K; Haglund C; Gunnarsson U

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Southern Hospital Trust, Kristiansand, Norway.

**RESUMEN / SUMMARY:** - BACKGROUND: To characterize the stage-specific prognostic relevance of preoperative systemic inflammatory response, defined by C-reactive protein (CRP), in colon cancer (CC) patients. MATERIAL AND METHODS: Data from CC patients operated on from 1998 to 2007 at three hospitals from three different Nordic countries were collected retrospectively from national registries, local databases and/or patient records. Patients with emergency surgery, infection or autoimmune disease were excluded. Associations between clinical or histopathological variables and CRP were assessed. Patients were followed from the date of surgery to death or end of follow-up. Disease-specific survival (DSS) was the main endpoint. RESULTS: In total, 525 patients with age and stage distributions which were

representative for CC patients were included. None of the patients was lost to follow-up. Age, TNM Stage, WHO differentiation grade and right-sided tumor location significantly associated with elevated CRP values, in contrast to postoperative morbidity, which did not. CRP levels were found to be a strong prognostic factor for DSS in CC. The risk of death due to CC was augmented with increasing levels of CRP in every stage of operated CC. Both short- and long-term DSS were impaired. The sub-hazard ratios for CRP-levels above 60 mg/L were 7.37 (CI 2.65-20.5) for stage I+ II, compared to 3.29 (CI 1.30-8.29) for stage III and 2.24 (CI 1.16-4.35) for stage IV. CONCLUSION: Increase of CRP concentrations correlate with clinically relevant poorer disease-specific survival in each stage of CC.

[534]

**TÍTULO / TITLE:** - Resveratrol induced ER expansion and ER caspase-mediated apoptosis in human nasopharyngeal carcinoma cells.

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

**REVISTA / JOURNAL:** - Apoptosis. 2013 Nov 22.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10495-013-0945-0](#)

**AUTORES / AUTHORS:** - Chow SE; Kao CH; Liu YT; Cheng ML; Yang YW; Huang YK; Hsu CC; Wang JS

**INSTITUCIÓN / INSTITUTION:** - Department of Nature Science Center for General Studies, Chang Gung University, Taoyuan, Taiwan, [chowse@mail.cgu.edu.tw](mailto:chowse@mail.cgu.edu.tw).

**RESUMEN / SUMMARY:** - Autophagy and endoplasmic reticulum (ER) stress response is important for cancer cells to maintain malignancy and resistance to therapy. trans-Resveratrol (RSV), a non-flavonoid agent, has been shown to induce apoptosis in human nasopharyngeal carcinoma (NPC) cells. In this study, the involvements of tumor-specific ER stress and autophagy in the RSV-mediated apoptosis were investigated. In addition to traditional autophagosomes, the images of transmission electron microscopy (TEM) indicated that RSV markedly induced larger, crescent-shaped vacuoles with single-layered membranes whose the expanded cisternae contains multi-lamellar membrane structures. Prolonged exposure to RSV induced a massive accumulation of ER expansion. Using an EGFP-LC3B transfection and confocal laser microscopy approach, we found RSV-induced EGFP-LC3 puncta co-localized with ER-tracker red dye, implicating the involvement of LC3II in ER expansion. The proapoptotic effect of RSV was enhanced after suppression of autophagy by ATG7 siRNA or blocking the autophagic flux by bafilomycin A1, but that was not changed after targeted silence of IRE1 or CHOP by siRNA. Using caspase inhibitors, we demonstrated the upregulation of caspase-12 (casp12) and the activation of casp4 were associated with the proapoptotic induction of RSV through the caspase-9/caspase-3 pathway. Intriguingly, siRNA knockdown of casp12, but not caspase-4, decreased the susceptibility of the NPC cells to RSV-mediated apoptosis. Further, we showed that RSV dose-dependently increased the ceramide accumulation as assessed by LC-MS/MS system. Using serine palmitoyltransferase (SPT, a key enzyme of de novo ceramide biosynthesis) inhibitors (L-cycloserine and myriocin), we found the increased ceramide accumulation was strongly correlated with the proapoptotic potential of RSV. This study revealed the ER expansion and upregulation of ER casp12 together may indicate profound biological effects of RSV and contributed to NPC cell

death. Targeting the different status of ER stress may provide a possible strategy for cancer treatments.

[535]

**TÍTULO / TITLE:** - CYP2C19 genotype-based phase I studies of a c-Met inhibitor tivantinib in combination with erlotinib, in advanced/metastatic non-small cell lung cancer.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Nov 26;109(11):2803-9. doi: 10.1038/bjc.2013.588. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.588](#)

**AUTORES / AUTHORS:** - Yamamoto N; Murakami H; Hayashi H; Fujisaka Y; Hirashima T; Takeda K; Satouchi M; Miyoshi K; Akinaga S; Takahashi T; Nakagawa K

**INSTITUCIÓN / INSTITUTION:** - Division of Thoracic Oncology, Shizuoka Cancer Center, 1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan.

**RESUMEN / SUMMARY:** - Background:A previous clinical study in non-small cell lung cancer (NSCLC) patients in Western countries suggested the potential for combination of a first-in-class non-ATP-competitive c-Met inhibitor tivantinib with an epidermal growth factor receptor-tyrosine kinase inhibitor erlotinib. Polymorphisms of CYP2C19, the key metabolic enzyme for tivantinib, should be addressed to translate the previous Western study to Asian population, because higher incidence of poor metabolisers (PMs) is reported in Asian population.Methods:Japanese patients with advanced/metastatic NSCLC received tivantinib in combination with erlotinib to evaluate safety and pharmacokinetics. Doses of tivantinib were escalated separately for extensive metabolisers (EMs) and PMs.Results:Tivantinib, when combined with erlotinib, was well tolerated up to 360 mg BID for EMs and 240 mg BID for PMs, respectively. Among 25 patients (16 EMs and 9 PMs), the adverse events (AEs) related to tivantinib and/or erlotinib (>20%, any grade) were rash, diarrhoea, dry skin and nausea. Grade  $\geq 3$  AEs were leukopenia, anaemia and neutropenia. No dose-limiting toxicity was observed. Pharmacokinetics profile of tivantinib was not clearly different between the combination and monotherapy. Three partial response and three long-term stable disease ( $\geq 24$  weeks) were reported.Conclusion:Two doses of tivantinib in combination with erlotinib were recommended based on CYP2C19 genotype: 360 mg BID for EMs and 240 mg BID for PMs.

[536]

**TÍTULO / TITLE:** - Expression of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Death Receptors DR4 and DR5 in Human Nonmelanoma Skin Cancer.

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

**REVISTA / JOURNAL:** - Am J Dermatopathol. 2013 Nov 6.

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

[1097/DAD.0b013e3182a3d31d](#)

**AUTORES / AUTHORS:** - Omran OM; Ata HS

**INSTITUCIÓN / INSTITUTION:** - \*Department of Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt; and daggerDepartment of Pathology, College of Medicine, Qassim University, Buridah, Qassim, Saudi Arabia.

**RESUMEN / SUMMARY:** - : Death receptors 4 and 5 (DR4 and DR5) are cell surface receptors that when activated by their ligand tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) triggers apoptosis in most cancer cells but not in normal cells. Currently, it remains unclear whether DR4 and DR5 are involved in immune surveillance against nonmelanoma skin cancer (NMSC) progression. The aim of this study was to investigate the expression of DR4 and DR5 in NMSC and relate the results to the established clinicopathologic prognostic factors. This study was conducted on about 80 skin specimens from patients with NMSC (40 basal cell carcinoma and 40 squamous cell carcinoma) and diagnosed and confirmed by biopsy. Immunohistochemical analysis for DR4 and DR5 was carried out on formalin-fixed paraffin-embedded sections of skin tissues using avidin-biotin peroxidase method. Significant expression of both DR4 and DR5 was observed in NMSC cases. There was statistically significant association between DR4 and DR5 expression in squamous cell carcinoma and each of tumor site and lymph node metastasis. There was statistically significant association between DR4 expression in basal cell carcinoma and histopathologic subtypes (high expression in nodular type) and between DR5 expression and tumor site (high expression in sun-exposed area). In conclusion, expression of TRAIL receptors that mediate extrinsic apoptotic pathway in NMSC may be suggestive of a reassessment of the suitability of TRAIL-based strategy in future NMSC therapies.

[537]

**TÍTULO / TITLE:** - Upregulation of the long non-coding rna hotair promotes esophageal squamous cell carcinoma metastasis and poor prognosis.

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

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 Nov;52(11):908-15. doi: 10.1002/mc.21944. Epub 2012 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1002/mc.21944](#)

**AUTORES / AUTHORS:** - Chen FJ; Sun M; Li SQ; Wu QQ; Ji L; Liu ZL; Zhou GZ; Cao G; Jin L; Xie HW; Wang CM; Lv J; De W; Wu M; Cao XF

**INSTITUCIÓN / INSTITUTION:** - Department of Surgical Oncology, Affiliated Nanjing Hospital of Nanjing Medical University and Oncology Center of Nanjing Medical University, Nanjing, Jiangsu, China.

**RESUMEN / SUMMARY:** - Recent studies of the individual functionalities of long non-coding RNAs (lncRNAs) in the development and progression of cancer have suggested that HOX transcript antisense RNA (HOTAIR) is capable of reprogramming chromatin organization and promoting cancer cell metastasis. In order to ascertain the expression pattern of the lncRNA HOTAIR and assess its biological role in the development and progression of esophageal squamous cell carcinoma (ESCC), HOTAIR expression in ESCC tissues and adjacent noncancerous tissues were collected from 78 patients and measured by real-time reverse transcription-polymerase chain reaction (RT-PCR). HOTAIR correlation with clinicopathological features and prognosis was also analyzed. Suppression of HOTAIR using siRNA treatment was performed in order to explore its role in tumor progression. Notably elevated HOTAIR expression levels were observed

in cancerous tissues compared to adjacent noncancerous tissues (96%,  $P < 0.01$ ), showing a high correlation with cancer metastasis ( $P < 0.01$ ), elevated TNM (2009) stage classification ( $P < 0.01$ ), and lowered overall survival rates ( $P = 0.003$ ). Multivariate analysis revealed that HOTAIR expression ( $P = 0.003$ ) is also an independent prognostic factor for comparison of TNM stage ( $P = 0.024$ ) and lymph node metastasis ( $P = 0.010$ ). Furthermore, in vitro assays of the ESCC cell line KYSE30 demonstrated that knockdown of HOTAIR reduced cell invasiveness and migration while increasing the response of cells to apoptosis. Thus, HOTAIR is a novel molecule involved in both ESCC progression and prognosis. Full elucidation of HOTAIR functionality relevant to ESCC may open avenues for the use of lncRNAs in identification of novel drug targets and therapies for ESCC and other prevalent cancers. © 2012 Wiley Periodicals, Inc.

[538]

**TÍTULO / TITLE:** - 18F-FDG PET/CT for Early Prediction of Response to Neoadjuvant Lapatinib, Trastuzumab, and Their Combination in HER2-Positive Breast Cancer: Results from Neo-ALTTO.

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

**REVISTA / JOURNAL:** - J Nucl Med. 2013 Nov;54(11):1862-8. doi: 10.2967/jnumed.112.119271. Epub 2013 Oct 3.

●● [Enlace al texto completo \(gratis o de pago\) 2967/jnumed.112.119271](#)

**AUTORES / AUTHORS:** - Gebhart G; Gamez C; Holmes E; Robles J; Garcia C; Cortes M; de Azambuja E; Fauria K; Van Dooren V; Aktan G; Coccia-Portugal MA; Kim SB; Vuylsteke P; Cure H; Eidtmann H; Baselga J; Piccart M; Flamen P; Di Cosimo S

**INSTITUCIÓN / INSTITUTION:** - Nuclear Medicine Department, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium.

**RESUMEN / SUMMARY:** - Molecular imaging receives increased attention for selecting patients who will benefit from targeted anticancer therapies. Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) enrolled 455 women with invasive human epidermal growth factor receptor 2 (HER2)-positive breast cancer and compared rates of pathologic complete response (pCR) to neoadjuvant lapatinib, trastuzumab, and their combination. Each anti-HER2 therapy was given alone for 6 wk, followed by 12 wk of the same therapy plus weekly paclitaxel. The early metabolic effects of the anti-HER2 therapies on the primary tumors and their predictive values for pCR were assessed in a subset of patients. METHODS: Eighty-six patients underwent (18)F-FDG PET/CT at baseline and weeks 2 and 6 of anti-HER2 treatment. An imaging core laboratory provided central validation, and 2 independent reviewers, masked to assigned treatment arm and clinical outcomes, performed consensus (18)F-FDG PET/CT readings. Maximum standardized uptake value (SUVmax) reductions from baseline were used to measure metabolic response. RESULTS: Seventy-seven of the 86 enrolled patients presented an evaluable baseline (18)F-FDG PET/CT scan; of these, 68 and 66 were evaluable at weeks 2 and 6, respectively. Metabolic responses in the primary tumors were evident after 2 wk of targeted therapy and correlated highly with metabolic responses at week 6 ( $R(2) = 0.81$ ). pCRs were associated with greater SUVmax reductions at both time points. Mean SUVmax reductions for pCR and non-pCR, respectively, were 54.3% versus 32.8% at week 2 ( $P = 0.02$ ) and 61.5% versus 34.1% at week 6 ( $P = 0.02$ ). (18)F-FDG PET/CT metabolic response rates at weeks 2

and 6 were 71.6% and 60%, respectively using European Organization for Research and Treatment of Cancer criteria; pCR rates were twice as high for (18)F-FDG PET/CT responders than nonresponders (week 2: 42% vs. 21%, P = 0.12; week 6: 44% vs. 19%, P = 0.05). CONCLUSION: Early metabolic assessment using (18)F-FDG PET/CT can identify patients with an increased likelihood of pCR after neoadjuvant trastuzumab, lapatinib, or their combination when given with chemotherapy.

[539]

**TÍTULO / TITLE:** - Circulating serum microRNAs as novel diagnostic and prognostic biomarkers for multiple myeloma and monoclonal gammopathy of undetermined significance.

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

**REVISTA / JOURNAL:** - Haematologica. 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.093500](#)

**AUTORES / AUTHORS:** - Kubiczkova L; Kryukov F; Slaby O; Dementyeva E; Jarkovsky J; Nekvindova J; Radova L; Greslikova H; Kuglik P; Vetesnikova E; Pour L; Adam Z; Sevcikova S; Hajek R

**INSTITUCIÓN / INSTITUTION:** - Department of Pathological Physiology, Faculty of Medicine, Masaryk University;

**RESUMEN / SUMMARY:** - Multiple myeloma still remains incurable in majority of cases prompting further search for new and better prognostic markers. Emerging evidence has suggested that circulating microRNAs can serve as minimally invasive biomarkers for multiple myeloma and monoclonal gammopathy of undetermined significance. In this study, a global analysis of serum microRNAs by TaqMan Low Density arrays was performed, followed by quantitative real-time PCR. The analyses revealed five deregulated microRNAs: miR-744, miR-130a, miR-34a, let-7d and let-7e in monoclonal gammopathy of undetermined significance, newly diagnosed and relapsed multiple myeloma when compared to healthy donors. Multivariate logistic regression analysis showed that combination of miR-34a and let-7e can distinguish multiple myeloma from healthy donors with sensitivity 80.6% and specificity 86.7% and monoclonal gammopathy of undetermined significance from healthy donors with sensitivity 91.1% and specificity 96.7%. Furthermore, lower levels of miR-744 and let-7e were associated with shorter overall survival and remission of myeloma patients. One-year mortality rate for miR-744 and let-7e was 41.9% and 34.6% for low expression and 3.3% and 3.9% for high expression group, respectively. Median time of remission for both miR-744 and let-7e was ~11 months for low expression and ~47 months for high expression groups of myeloma patients. These data demonstrate that expression patterns of circulating microRNAs are altered in multiple myeloma and monoclonal gammopathy of undetermined significance and miR-744 with let-7e are associated with survival of myeloma patients.

[540]

**TÍTULO / TITLE:** - NF-kappaB activation was involved in reactive oxygen species-mediated apoptosis and autophagy in 1-oxoeudesm-11(13)-eno-12,8alpha-lactone-treated human lung cancer cells.

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

**REVISTA / JOURNAL:** - Arch Pharm Res. 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1007/s12272-013-0270-8](http://1007/s12272-013-0270-8)

**AUTORES / AUTHORS:** - Liu S; Wu D; Li L; Sun X; Xie W; Li X

**INSTITUCIÓN / INSTITUTION:** - School of Ocean, Shandong University, Weihai, 264209, People's Republic of China.

**RESUMEN / SUMMARY:** - 1-oxoeudesm-11(13)-eno-12,8alpha-lactone (OEL), a novel eudesmane-type sesquiterpene compound, has been shown to inhibit the growth of some cancer cell lines and induce significant apoptosis. Here, we investigated the anti-cancer activities of OEL in human lung cancer cells. Our studies demonstrated that OEL induced both apoptosis and autophagy in A549 and H460 cells. OEL-induced autophagy was assessed by appearance of autophagic vacuoles, formation of acidic vesicular organelles, conversion of LC3-I to LC3-II, recruitment of LC3-II to the autophagosomes, and activation of autophagy genes. Furthermore, administration of autophagic inhibitor 3-methyladenine augments OEL-induced apoptotic cell death. The induction of autophagy and apoptosis by OEL links to NF-kappaB activation and the generation of reactive oxygen species (ROS). Interruption of NF-kappaB activation by specific inhibitor promotes apoptosis, but decreases autophagy. ROS antioxidants (N-acetylcysteine) attenuated both OEL-induced autophagy and apoptosis. Further experiments confirmed that OEL-induced activation of ROS was increased by NF-kappaB inhibitor whereas NF-kappaB activation was not affected by ROS inhibition. These findings suggest that OEL-elicited autophagic response plays a protective role that impedes cell death, and inhibition of autophagy could be an adjunctive strategy for enhancing the chemotherapeutic effect of OEL as an antitumor agent.

[541]

**TÍTULO / TITLE:** - Changes in signaling pathways induced by vandetanib in a human medullary thyroid carcinoma model, as analyzed by Reverse Phase Protein Array.

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

**REVISTA / JOURNAL:** - Thyroid. 2013 Nov 20.

●● Enlace al texto completo (gratis o de pago) [1089/thy.2013.0514](http://1089/thy.2013.0514)

**AUTORES / AUTHORS:** - Broutin S; Commo F; De Koning L; Marty-Prouvost B; Lacroix L; Talbot M; Caillou B; Dubois T; Ryan AJ; Dupuy C; Schlumberger M; Bidart JM

**INSTITUCIÓN / INSTITUTION:** - Institut Gustave-Roussy, Departement de Biologie et Pathologie Medicales, 114 rue Edouard Vaillant, Villejuif, France, 94805, 0033142114057, 0031142114401 ; [broutin@igr.fr](mailto:broutin@igr.fr).

**RESUMEN / SUMMARY:** - Background: Medullary thyroid carcinoma (MTC) is a rare tumor that is caused by activating mutations in the proto-oncogene RET. Vandetanib, a tyrosine-kinase inhibitor, has been recently approved to treat adult patients with metastatic MTC. The aim of this study was to investigate changes in signaling pathways induced by vandetanib treatment in preclinical MTC models, using the reverse-phase protein array method (RPPA). Methods: The human TT cell line was used to assess in vitro and in vivo activity of vandetanib. Protein extracts from TT cells or TT xenografted mice, treated by increasing concentrations of vandetanib for different periods of time, were probed with a set of 12 antibodies representing major signaling pathways, using RPPA. Results were validated using two distinct protein detection methods, western immunoblotting and immunohistochemistry. Results: Vandetanib displays antiproliferative and antiangiogenic activities and inhibits RET auto-

phosphorylation. The MAPK and AKT pathways were the two major signaling pathways inhibited by vandetanib. Interestingly, phosphorylated levels of NFkappaB-p65 were significantly increased by vandetanib. Comparable results were obtained in both the in vitro and in vivo approaches as well as for the protein detection methods. However, some discrepancies were observed between RPPA and western immunoblotting, possibly due to lack of specificity of the primary antibodies used. Conclusions: Overall, our results confirmed the interest of RPPA for screening global changes induced in signaling pathways by kinase inhibitors. MAPK and AKT were identified as the main pathways involved in vandetanib response in MTC models. Our results also suggest alternative routes for controlling the disease and provide a rationale for the development of therapeutic combinations based on the comprehensive identification of molecular events induced by inhibitors.

[542]

**TÍTULO / TITLE:** - Inhibition of proliferation and invasiveness of ovarian cancer C13\* cells by a poly(ADP-ribose) polymerase inhibitor and the role of nuclear factor-kappaB.

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

**REVISTA / JOURNAL:** - J Int Med Res. 2013 Oct;41(5):1577-85. doi: 10.1177/0300060513480913.

●● Enlace al texto completo (gratis o de pago) [1177/0300060513480913](#)

**AUTORES / AUTHORS:** - Wang Z; Li Y; Lv S; Tian Y

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynaecology, Shandong University Affiliated Provincial Hospital, Jinan, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: To investigate the effect of the poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor PJ34 on the proliferation and invasiveness of ovarian cancer C13\* cells and the role of nuclear factor-kappaB (NF-kappaB). METHODS: Proliferation of C13\* cells was measured using a 3-(4,5-dimethylthazol-2-yl)-2,5-diphenyl tetrazolium bromide assay after incubation with PJ34 at different concentrations and for different treatment durations. In addition, expression of PARP-1 and the NF-kappaB p65 subunit after treatment with PJ34 was measured using Western blot and immunocytochemistry. The effect of PJ34 on cell invasiveness was examined using a transwell invasion assay. RESULTS: PJ34 inhibited proliferation of C13\* cells in a time- and dose-dependent manner. PJ34 treatment was also associated with a dose-dependent decrease in PARP-1 and NF-kappaB p65 expression and attenuated invasiveness of C13\* cells. PARP-1 expression was positively correlated with NF-kappaB p65 expression. CONCLUSION: The PARP-1 inhibitor PJ34 can markedly inhibit the proliferation and invasiveness of C13\* cells, possibly due to PARP-1-mediated attenuation of NF-kappaB activity.

[543]

**TÍTULO / TITLE:** - Truncation of inhibitor of growth family protein 5 effectively induces senescence, but not apoptosis in human tongue squamous cell carcinoma cell line.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 20.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1410-y](#)

**AUTORES / AUTHORS:** - Qi L; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Orthodontics, School of Stomatology, China Medical University, Shenyang, Liaoning, China.

**RESUMEN / SUMMARY:** - In these studies, inhibitor of growth protein 5 (ING5) and various fragments of it were overexpressed in the human tongue squamous cell carcinoma cell line, HSC-3. The roles of ING5 in HSC-3 cells were then identified in vitro. Our results indicate that intact ING5 can inhibit proliferation and induce apoptosis in HSC-3 cells. Moreover, two truncated fragments of ING5 (aa 1-184 and aa 107-226) can induce cellular senescence. To analyze the signaling pathway involved, western blotting was performed. In these assays, two truncated fragments of ING5 were found to inhibit the cyclin E and CDK2 expression. These results are consistent with the S phase arrest observed with the overexpression of truncated ING5. However, the mechanisms of ING5-induced cellular senescence remain unclear, and extensive investigations are required in future studies.

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[544]

**TÍTULO / TITLE:** - INCB018424 induces apoptotic cell death through the suppression of pJAK1 in human colon cancer cells.

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

**REVISTA / JOURNAL:** - Neoplasma. 2014;61(1):56-62.

**AUTORES / AUTHORS:** - An HJ; Choi EK; Kim JS; Hong SW; Moon JH; Shin JS; Ha SH; Kim KP; Hong YS; Lee JL; Choi EK; Lee JS; Jin DH; Kim TW

**RESUMEN / SUMMARY:** - Janus kinase (JAK) is one of the main upstream activators of signal transducers and activators of transcription (STAT) that are constitutively activated in various malignancies and are associated with cell growth, survival, and carcinogenesis. Here, we investigated the role of JAKs in colorectal cancer in order to develop effective therapeutic targets for INCB018424, which is the first JAK1/2 inhibitor to be approved by FDA. After examining the basal expression levels of phospho-JAK1 and phospho-JAK2, we measured the effects of INCB018424 on the phosphorylation of JAK1/2 using western blot analysis. Cell viability was determined using the trypan blue exclusion assay. The cell death mechanism was identified by the activation of caspase 3 using western blot and annexin V staining. The basal levels of phospho-JAK1 and phospho-JAK2 were cancer cell type dependent. Colorectal cancer cell lines that phosphorylate both JAK1 and JAK2 include DLD-1 and RKO. INCB018424 inactivates both JAK1 and JAK2 in DLD-1 cells but inactivates only JAK1 in RKO cells. Cell death was proportional to the inactivation of JAK1 but not JAK2. INCB018424 causes caspase-dependent cell death, which is prevented by treatment with z-VAD. The inhibition of JAK1 phosphorylation seemed sufficient to allow INCB018424-mediated apoptosis. JAK1 is a key molecule that is involved in colon cancer cell survival and the inhibition of JAK1 by INCB018424 results in caspase-dependent apoptosis in colorectal cancer cells. The use of selective JAK1 inhibitors could be an attractive therapy against colorectal cancer, but further clinical investigations are needed to test this possibility. Keywords: INCB018424; JAK; apoptosis; colon cancer.

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[545]

**TÍTULO / TITLE:** - Nexrutine Inhibits Survival and Induces G1 Cell Cycle Arrest, Which Is Associated with Apoptosis or Autophagy Depending on the Breast Cancer Cell Line.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Nov 9.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.780627](#)

**AUTORES / AUTHORS:** - Yan G; Lanza-Jacoby S; Wang C

**INSTITUCIÓN / INSTITUTION:** - a Department of Surgery , Thomas Jefferson University , Philadelphia , Pennsylvania , USA.

**RESUMEN / SUMMARY:** - Breast cancers that are estrogen receptor (ER) negative or are ER negative with ErbB2/HER-2 overexpression have a poor prognosis, which emphasizes the importance of developing compounds for preventing breast cancer. Nexrutine, an herbal extract from the plant Phellodendron amurense, has been used for centuries in Asian medicine to treat inflammation, gastroenteritis, abdominal pain, and diarrhea. In this study we investigated the anticancer effects of Nexrutine on ER negative breast cancer cell lines that are positive or negative for HER-2. Nexrutine decreased the activities of 2 potential targets of breast cancer, cyclooxygenase (COX)-2, and peroxisome proliferators activated receptor gamma (PPARgamma). The antiinflammatory effects of Nexrutine were evident with decreased prostaglandin (PG)E2 production, protein expression of microsomal PGE2 synthase (mPGES), and PPARgamma. Nexrutine decreased cell survival and induced a G1 cell cycle arrest in SkBr3 and MDA-MB 231 cells, which were associated with reduced protein expression of Cyclin D1 and cdk2 along with increased protein expression of p21 and p27. The growth-inhibitory effect of Nexrutine was associated with apoptosis in SkBr3 cells and autophagy in MDA-MB231 cells. Based on these findings, we propose that Nexrutine may provide a novel approach for protection against breast cancer.

[546]

**TÍTULO / TITLE:** - Antitumor activity of an enzyme prodrug therapy targeted to the breast tumor vasculature.

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

**REVISTA / JOURNAL:** - Cancer Invest. 2013 Oct;31(8):505-10. doi: 10.3109/07357907.2013.840383.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.840383](#)

**AUTORES / AUTHORS:** - Van Rite BD; Krais JJ; Cherry M; Sikavitsas VI; Kurkjian C; Harrison RG

**INSTITUCIÓN / INSTITUTION:** - 1Bioengineering Center and the School of Chemical, Biological and Materials Engineering, University of Oklahoma , Norman, Oklahoma , USA.

**RESUMEN / SUMMARY:** - The L-methioninase-annexin V/selenomethionine enzyme prodrug system, designed to target the tumor vasculature and release the methylselenol anticancer drug in the tumor, was tested in mice with implanted MBA-MB-231 breast tumors. This therapy was able to cause a reduction in the size of the tumors during the treatment period. It was shown that L-methioninase-annexin V was uniformly bound at the blood vessel surface in the tumor and also that there was a substantial cutoff of blood flowing through the treated tumor, consistent with the therapy's design. This new approach for enzyme prodrug therapy of breast cancer appears promising.

[547]

**TÍTULO / TITLE:** - DNA copy number aberrations in endobronchial lesions: a validated predictor for cancer.

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

**REVISTA / JOURNAL:** - Thorax. 2013 Nov 13. doi: 10.1136/thoraxjnl-2013-203821.

●● Enlace al texto completo (gratis o de pago) [1136/thoraxjnl-2013-203821](#)

**AUTORES / AUTHORS:** - van Boerdonk RA; Daniels JM; Snijders PJ; Grunberg K; Thunnissen E; van de Wiel MA; Ylstra B; Postmus PE; Meijer CJ; Meijer GA; Smit EF; Sutedja TG; Heideman DA

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, VU University Medical Center, , Amsterdam, The Netherlands.

**RESUMEN / SUMMARY:** - We recently identified a DNA copy number aberration (CNA)-based classifier, including changes at 3p26.3-p11.1, 3q26.2-29, and 6p25.3-24.3, as a risk predictor for cancer in individuals presenting with endobronchial squamous metaplasia. The current study was set out to validate the prediction accuracy of this classifier in an independent series of endobronchial squamous metaplastic and dysplastic lesions. The study included 36 high-risk subjects who had endobronchial lesions of various histological grades that were identified and biopsied by autofluorescence bronchoscopy and were subjected to arrayCGH in a nested case-control design. Of the 36 patients, 12 had a carcinoma in situ or invasive carcinoma at the same site at follow-up (median 11 months, range 4-24), while 24 controls remained cancer free (78 months, range 21-142). The previously defined CNA-based classifier demonstrated 92% (95% CI 77% to 98%) accuracy for cancer (in situ) prediction. All nine subjects with CNA-based classifier-positive endobronchial lesions at baseline experienced cancer outcome, whereas all 24 controls and 3 cases were classified as being low risk. In conclusion, CNAs prove to be a highly accurate biomarker for assessing the progression risk of endobronchial squamous metaplastic and dysplastic lesions. This classifier could assist in selecting subjects with endobronchial lesions who might benefit from more aggressive therapeutic intervention or surveillance.

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[548]

**TÍTULO / TITLE:** - A novel acidic serine protease, ASPNJ inhibits proliferation, induces apoptosis and enhances chemo-susceptibility of acute promyelocytic leukemia cell.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Dec;37(12):1697-703. doi: 10.1016/j.leukres.2013.09.017. Epub 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.09.017](#)

**AUTORES / AUTHORS:** - Ge X; Bo Q; Hong X; Cui J; Jiang X; Hong M; Liu J

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, Norman Bethune College of Medicine, Jilin University, Changchun, Jilin, China; Laboratory of Metabolic Disease Research and Drug Development, China Medical University, Shenyang, China.

**RESUMEN / SUMMARY:** - Acidic serine protease (ASPNJ) purified from *Neanthes japonica*, is a fibrinolytic enzyme. Earthworm fibrinolytic enzyme has been recently reported with anti-tumor activity on human hepatoma cells. To investigate if ASPNJ play therapeutic effects on emergent blood cancer, acute promyelocytic leukemia (APL), we tested the effects of ASPNJ on APL cell line NB4. Our results showed that ASPNJ inhibited the growth of NB4 cells in a dose and time dependent manner. Cell

apoptosis was induced by ASPNJ with obvious morphological changes. The sensitivity of cells to cytarabine and doxorubicin were greatly increased respectively by combination with ASPNJ. In contrast to inhibitory effects on NB4 cells, ASPNJ showed much less effect on normal human neutrophils survival. There were no effects of hemolysis and agglutination observed on normal human erythrocytes following ASPNJ treatment. Conclusively, our data suggest that ASPNJ may become a new candidate for leukemia therapeutic approaches.

[549]

**TÍTULO / TITLE:** - Clonal evolution in chronic lymphocytic leukemia detected by fluorescence in situ hybridization and conventional cytogenetics after stimulation with CpG oligonucleotides and interleukin-2: A prospective analysis.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Oct 29. pii: S0145-2126(13)00374-3. doi: 10.1016/j.leukres.2013.10.019.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.10.019](#)

**AUTORES / AUTHORS:** - Brejcha M; Stoklasova M; Brychtova Y; Panovska A; Stepanovska K; Vankova G; Plevova K; Oltova A; Horka K; Pospisilova S; Mayer J; Doubek M

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Hospital Novy Jicin, Czech Republic.

**RESUMEN / SUMMARY:** - Chronic lymphocytic leukemia (CLL) patients may acquire new chromosome abnormalities during the course of their disease. Clonal evolution (CE) has been detected by conventional chromosome banding (CBA), several groups also confirmed CE with fluorescence in situ hybridization (FISH). At present, there are minimal prospective data on CE frequency determined using a combination of both methods. Therefore, the aim of our study was to prospectively assess CE frequency using a combination of FISH and CBA after stimulation with CpG oligonucleotides and interleukin-2. Between 2008 and 2012, we enrolled 140 patients with previously untreated CLL in a prospective trial evaluating CE using FISH and CBA after stimulation. Patients provided baseline and regular follow-up peripheral blood samples for testing. There was a median of 3 cytogenetic examinations (using both methods) per patient. CE was detected in 15.7% (22/140) of patients using FISH, in 28.6% (40/140) using CBA, and in 34.3% (48/140) of patients by combining both methods. Poor-prognosis CE (new deletion 17p, new deletion 11q or new complex karyotype) was detected in 15% (21/140) of patients and was significantly associated with previous CLL treatment ( $p=0.013$ ). CBA provides more complex information about cytogenetic abnormalities in CLL patients than FISH and confirms that many patients can acquire new abnormalities during the course of their disease in a relatively short time period.

[550]

**TÍTULO / TITLE:** - Can FDG-PET/CT predict early response to neoadjuvant chemotherapy in breast cancer?

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

**REVISTA / JOURNAL:** - Eur J Surg Oncol. 2013 Dec;39(12):1358-63. doi: 10.1016/j.ejso.2013.08.025. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejso.2013.08.025](http://1016/j.ejso.2013.08.025)

**AUTORES / AUTHORS:** - Andrade WP; Lima EN; Osorio CA; do Socorro Maciel M; Baiocchi G; Bitencourt AG; Fanelli MF; Damascena AS; Soares FA

**INSTITUCIÓN / INSTITUTION:** - Department of Breast Surgery, A.C. Camargo Cancer Hospital, Sao Paulo, Brazil. Electronic address: [wesley.andrade@hotmail.com](mailto:wesley.andrade@hotmail.com).

**RESUMEN / SUMMARY:** - PURPOSE: Neoadjuvant chemotherapy (NAC) in breast cancer is currently used not only for locally advanced tumors, but also for large operable tumors when breast preservation is considered. It also provides the opportunity to evaluate chemotherapy tumor response. Our aim was to correlate the relative change in the standardized uptake value (SUV) of (18)F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET/CT) with pathologic response after NAC. METHODS: We prospectively evaluated 40 patients with invasive ductal breast carcinomas from February 2010 to December 2011. FDG-PET/CT was performed at baseline and after the second cycle of NAC. All patients underwent surgery after NAC. Pathologic response was evaluated according to Residual Cancer Burden (RCB) index. RESULTS: The mean age was 41.9 years. Median primary tumor size was 6 cm. Pathologic complete response (pCR) was obtained in 12 (30%) patients. The tumor baseline mean maximum SUV (SUVmax), and after second cycle were: 8.97 (sd.4.3) and 4.07 (sd.3.2), respectively. The relative change (DeltaSUV) after the second course of NAC was significantly higher for patients with pCR (-81.58%) when compared to the non-pCR patients (-40.18%) (p = 0.001). The optimal DeltaSUV threshold that discriminates between pCR and non-pCR was -71.8% (83.3% sensitivity; 78.5% specificity). Moreover, the optimal DeltaSUV threshold to discriminate between NAC responders and non-responders was -59.1% (68% sensitivity; 75.0% specificity). CONCLUSIONS: Our data suggest that the FDG-PET/CT DeltaSUV after the second course of NAC can predict pathological response in ductal breast carcinomas, and potentially identify a subgroup of non-responding patients for whom ineffective chemotherapy should be avoided. SYNOPSIS: Breast cancer is the most frequently diagnosed cancer in women. The indications for neoadjuvant chemotherapy are increasing. Early information on chemotherapy response is crucial and methods that predict the therapeutic effectiveness might avoid potentially ineffective chemotherapies in non-responding patients.

[551]

**TÍTULO / TITLE:** - Interleukin-2 priming chemotherapy: A strategy to improve the remission of refractory/relapsed T cell acute lymphoblastic leukemia.

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

**REVISTA / JOURNAL:** - Med Hypotheses. 2013 Nov;81(5):878-80. doi: 10.1016/j.mehy.2013.08.037. Epub 2013 Sep 11.

●● Enlace al texto completo (gratis o de pago) [1016/j.mehy.2013.08.037](http://1016/j.mehy.2013.08.037)

**AUTORES / AUTHORS:** - Zhang C; Zhang X; Chen XH

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, People's Republic of China. Electronic address: [chzhang2003@tom.com](mailto:chzhang2003@tom.com).

**RESUMEN / SUMMARY:** - Regardless of the salvage therapy used, primary induction failure in acute lymphoblastic leukemia (refractory ALL) and relapse after a complete remission (CR) are associated with dismal outcomes. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) may be the best treatment option for relapsed/refractory ALL. However, the outcome of allo-HSCT is very poor when a patient is not in CR. Quiescent leukemia cells protect them from the commonly used cell cycle-specific chemotherapeutic agents. Interleukin-2 (IL-2), a very well characterized T cell growth factor, is responsible for the progression of T lymphocytes from the G0 to the S phase of the cell cycle. IL-2 receptors are present on malignant T cells. Interaction of IL-2 with the IL-2 receptor triggers T cell proliferation, but T cells must change from a resting to an activated state, which leads to the de novo synthesis of IL-2 and expression of the IL-2 receptor. Thus, exogenous IL-2 administration is pivotal for the activation of T cells. Based on the findings above mentioned, we hypothesized that IL-2 priming chemotherapy improves the remission of refractory/relapsed T cell acute lymphoblastic leukemia.

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[552]

**TÍTULO / TITLE:** - The prognostic value of glycerol-3-phosphate dehydrogenase 1-like expression in head and neck squamous cell carcinoma.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Aug 19. doi: 10.1111/his.12258.

●● [Enlace al texto completo \(gratis o de pago\) 1111/his.12258](#)

**AUTORES / AUTHORS:** - Feng Z; Li JN; Wang L; Pu YF; Wang Y; Guo CB

**INSTITUCIÓN / INSTITUTION:** - Department of Oral and Maxillofacial Surgery, School of Stomatology, PekingUniversity, Beijing, China.

**RESUMEN / SUMMARY:** - AIMS: In this study, we sought to determine the prognostic significance of glycerol-3-phosphate dehydrogenase 1-like (GPD1L) expression in head and neck squamous cell carcinoma (HNSCC). METHODS AND RESULTS: The mRNA levels of GPD1L were measured in 70 paired HNSCC and corresponding adjacent normal tissues using real-time PCR. GPD1L protein levels were evaluated in HNSCC from 135 patients using immunohistochemical staining. Correlations were analysed between GPD1L levels and local recurrence rate, regional recurrence rate, second primary malignancy rate), disease-free survival (DFS) and disease-specific survival (DSS). The results of real-time PCR showed that, compared with the paired normal tissues, mRNA levels of GPD1L were decreased significantly in HNSCC ( $P < 0.001$ ). Patients whose tumours showed high GPD1L protein expression had a significantly better prognosis than those whose tumours showed low expression (61.3% versus 21.4%,  $P < 0.001$  for DFS; 68% versus 39.3%,  $P = 0.001$  for DSS). High GPD1L expression was associated with a lower local recurrence rate than low GPD1L expression ( $P = 0.049$ ). Multivariate survival analysis also showed that GPD1L expression was an independent prognostic factor ( $P = 0.001$ ). CONCLUSIONS: Our results indicate that the GPD1L expression is a strong predictor for local recurrence and survival in HNSCC.

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[553]

**TÍTULO / TITLE:** - Gain of Function of Mutant TP53 in Glioblastoma: Prognosis and Response to Temozolomide.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Nov 19.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3380-0](#)

**AUTORES / AUTHORS:** - Wang X; Chen JX; Liu JP; You C; Liu YH; Mao Q

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, West China Hospital of Sichuan University, Chengdu, China, [wangxiangtim@gmail.com](mailto:wangxiangtim@gmail.com).

**RESUMEN / SUMMARY:** - PURPOSE: Our aim was to investigate the relationship between mutant p53 and the prognosis of malignant glioma treated with temozolomide, and the regulation of mutant TP53 induced drug resistance, by molecular experimentation and a clinical trial. METHODS: Adult patients with newly surgical diagnosed glioblastoma were randomly assigned to receive either temozolomide or semustine after radiation treatment. The statuses of TP53 and expression of TP53 and O6-methylguanine DNA-methyltransferase (MGMT) were determined retrospectively in tumor tissue from enrolled patients. The primary end point was overall survival. Synthetic small interfering RNA was used to knock down mutant TP53 in T98G and U138 cells, which are human glioblastoma cells with a P53 mutation, by screening of exons 4-8. Viable cell survival was measured when these cells were exposed to temozolomide or semustine. Expression of MGMT at the messenger RNA level was also determined. RESULTS: The overall survival was 34.3 % at 2 years, 22.9 % at 3 years, 11.4 % at 4 years, and 8.6 % at 5 years with temozolomide, versus 18.2, 12.1, 3.0, and 0 %, respectively, with semustine. TP53 mutation and expression of mutant TP53 and MGMT showed significant inverse correlations with overall survival. Knockdown of mutant TP53 led to a fivefold increase in chemosensitivity to temozolomide but not semustine. Mutant TP53 knockdown induced down-regulation of MGMT expression. CONCLUSIONS: Mutant TP53 is strongly associated with a poor prognosis for overall survival in patients with glioblastoma. Also, TP53 mutation may decrease the chemosensitivity of glioblastoma to temozolomide by increasing MGMT expression.

[554]

**TÍTULO / TITLE:** - Resveratrol suppresses cancer cell glucose uptake by targeting reactive oxygen species-mediated hypoxia-inducible factor-1alpha activation.

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

**REVISTA / JOURNAL:** - J Nucl Med. 2013 Dec;54(12):2161-7. doi: 10.2967/jnumed.112.115436. Epub 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [2967/jnumed.112.115436](#)

**AUTORES / AUTHORS:** - Jung KH; Lee JH; Thien Quach CH; Paik JY; Oh H; Park JW; Lee EJ; Moon SH; Lee KH

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - Resveratrol is gaining attention for its anticancer effects and is also recognized for its antioxidant properties and influence on glucose metabolism. Augmented reactive oxygen species (ROS) and high glycolytic flux are common characteristics of malignant cells. We thus evaluated the effect of resveratrol on cancer cell glucose metabolism and investigated the role of ROS in the response. METHODS:

Cancer cells were measured for cell content and (18)F-FDG uptake. Assays were performed for lactate production; hexokinase activity and intracellular ROS; and immunoblotting for hypoxia-inducible factor-1alpha (HIF-1alpha), Akt, mammalian target of rapamycin, and glucose transporter type 1 (Glut-1). Animal studies were performed with small-animal PET imaging of Lewis lung carcinoma tumor-bearing mice. RESULTS: Resveratrol mildly decreased cell content and more pronouncedly suppressed (18)F-FDG uptake in Lewis lung carcinoma, HT-29 colon, and T47D breast cancer cells. Hence, (18)F-FDG uptake normalized to cell content was reduced to less than half of controls by 24-h exposure to resveratrol. This reduction was attributed to reduced glycolytic flux and Glut-1 expression. Resveratrol also decreased intracellular ROS in patterns that closely paralleled (18)F-FDG uptake. Scavenging of ROS with N-acetyl cysteine, but not inhibition of nicotinamide adenine dinucleotide phosphate oxidase, was sufficient to suppress (18)F-FDG uptake. Conversely, ROS inducers effectively reversed the metabolic response of resveratrol. HIF-1alpha protein was markedly reduced by resveratrol, and inhibiting HIF-1alpha expression with cycloheximide or specific small interfering RNAs suppressed (18)F-FDG uptake. The proteosomal inhibitor MG132 partly restored HIF-1alpha level and (18)F-FDG uptake in resveratrol-treated cells. Resveratrol also inhibited Akt activation; in addition, inhibitors and small interfering RNAs against phosphoinositide 3-kinase decreased (18)F-FDG uptake. Finally, small-animal PET results showed resveratrol treatment to suppress tumor (18)F-FDG uptake in vivo. CONCLUSION: Resveratrol suppresses cancer cell (18)F-FDG uptake and glycolytic metabolism in a manner that depends on the capacity of resveratrol to inhibit intracellular ROS, which downregulates HIF-1alpha accumulation.

[555]

**TÍTULO / TITLE:** - "To Serve and Protect": Enzyme Inhibitors as Radiopeptide Escorts Promote Tumor Targeting.

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

**REVISTA / JOURNAL:** - J Nucl Med. 2013 Nov 28.

●● Enlace al texto completo (gratis o de pago) [2967/jnumed.113.129411](#)

**AUTORES / AUTHORS:** - Nock BA; Maina T; Krenning EP; de Jong M

**INSTITUCIÓN / INSTITUTION:** - Molecular Radiopharmacy, INRASTES, National Center for Scientific Research "Demokritos," Athens, Greece.

**RESUMEN / SUMMARY:** - Radiolabeled octreotide analogs are most successfully being applied today in clinical cancer imaging and treatment. Propagation of this paradigm to other radiopeptide families has been greatly hampered by the inherent poor metabolic stability of systemically administered peptide analogs. We hypothesized that the in vivo coadministration of specific enzyme inhibitors would improve peptide bioavailability and hence tumor uptake. Through single coinjection of the neutral endopeptidase inhibitor phosphoramidon (PA), we were able to provoke remarkable rises in the percentages of circulating intact somatostatin, gastrin, and bombesin radiopeptides in mouse models, resulting in a remarkable increase in uptake in tumor xenografts in mice. METHODS: The peptide conjugates [DOTA-Ala1]SS14 (DOTA-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys]-OH), PanSB1 (DOTA-PEG2-dTyr-Gln-Trp-Ala-Val-betaAla-His-Phe-Nle-NH2), and DOTA-MG11 (DOTA-dGlu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH2) were labeled with 111In by 20 min of heating at an acidic

pH. Metabolic stability was studied with high-performance liquid chromatography analysis of blood samples collected 5 min after the injection of the test radiopeptide alone or with PA into mice. Biodistribution was studied after injection of each <sup>111</sup>In-labeled radiopeptide alone or after coinjection of PA in tumor-bearing severe combined immunodeficient (SCID) mice. RESULTS: The amount of intact [<sup>111</sup>In-DOTA-Ala1]SS14 detected in the mouse circulation at 5 min after the injection of PA increased impressively-from less than 2% to 86%-whereas the uptake in AR4-2J xenografts rose from less than 1 percentage injected dose per gram of tissue (%ID/g) to 14 %ID/g at 4 h after injection. Likewise, the coadministration of PA resulted in a marked increase in the amount of circulating intact <sup>111</sup>In-PanSB1-from 12% to 80%-at 5 min after injection, and radioligand uptake in human PC-3 xenografts in SCID mice escalated from less than 4 %ID/g to greater than 21 %ID/g at 4 h after injection. In a similar manner, the coadministration of PA resulted in an equally impressive increase in intact [<sup>111</sup>In-DOTA]MG11 levels in the mouse bloodstream-from less than 5% to 70%-at 5 min after injection, leading to a remarkable increase in radiotracer uptake-from 2 %ID/g to greater than 15 %ID/g-in both AR4-2J tumors and A431(CCKR+) tumors (i.e., tumors induced by A431 cells transfected to stably express the human cholecystinin subtype 2 receptor) in mice at 4 h after injection. This effect was well visualized by SPECT/CT imaging of AR4-2J tumor-bearing mice at 4 h after injection. CONCLUSION: The results of this study clearly demonstrate that the coadministration of key enzyme inhibitors can effectively prolong the survival of radiolabeled peptides in the circulation, securing their safe transit to the target. This strategy clearly provoked an unprecedented increase in radiolabel accumulation in tumor xenografts in mice; this increase might translate into higher diagnostic sensitivity or improved therapeutic efficacy of radiopeptide drugs in cancer patients. Hence, our findings provide exciting new opportunities for the application of biodegradable (radio)peptide drugs of either natural or synthetic origin as well as for the rationale design of analogs that are stable in vivo.

[556]

**TÍTULO / TITLE:** - p75 neurotrophin receptor and fenretinide-induced signaling in neuroblastoma.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 20.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2355-y](#)

**AUTORES / AUTHORS:** - Ganeshan VR; Schor NF

**INSTITUCIÓN / INSTITUTION:** - Center for Neural Development and Disease, University of Rochester Medical Center, Rochester, NY, 14642, USA.

**RESUMEN / SUMMARY:** - PURPOSE: Neuroblastoma is the most common extracranial solid tumor of childhood. The retinoic acid analogue, fenretinide (4-hydroxyphenyl retinamide; 4-HPR), induces apoptosis in neuroblastoma cells in vitro and is currently in clinical trials for children with refractory neuroblastoma. We have previously shown that expression of the p75 neurotrophin receptor (p75NTR) enhances apoptosis induction and mitochondrial accumulation of reactive oxygen species by 4-HPR in neuroblastoma cells. We now examine the signaling events that underlie this effect. METHODS: Systematic examination of pro- and anti-apoptotic signaling effectors was performed by Western blot. Specific inhibitors of JNK phosphorylation and scavengers

of mitochondrial reactive oxygen species were used to demonstrate the roles of these phenomena in the enhancement of fenretinide efficacy. RESULTS: The present studies demonstrate that enhancement of 4-HPR-induced apoptosis by p75NTR is dependent upon p38MAPK phosphorylation, JNK phosphorylation, caspase 3 activation, Akt cleavage, and decreased Akt phosphorylation. In addition, treatment with 4-HPR results in upregulation of MKK4 and MEKK1, and phosphorylation of MKK3/6. Efforts to enhance the efficacy of 4-HPR and to identify those tumors most likely to respond to it might exploit these effectors of 4-HPR-induced apoptosis. CONCLUSIONS: Pharmacological agents that enhance MKK4 or MEKK1 expression or JNK expression or phosphorylation may enhance efficacy of 4-HPR in neuroblastomas that do not express high levels of p75NTR.

[557]

**TÍTULO / TITLE:** - Prognostic value of epidermal growth factor receptor mutations in resected lung adenocarcinomas.

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

**REVISTA / JOURNAL:** - Med Oncol. 2014 Jan;31(1):771. doi: 10.1007/s12032-013-0771-9. Epub 2013 Nov 19.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12032-013-0771-9](#)

**AUTORES / AUTHORS:** - Liu WS; Zhao LJ; Pang QS; Yuan ZY; Li B; Wang P

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Cancer Prevention and Therapy, Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, 300060, China.

**RESUMEN / SUMMARY:** - The purpose of this study was to evaluate the association between epidermal growth factor receptor (EGFR) mutations and prognosis in patients with completely resected lung adenocarcinoma. A total of 131 patients were included in this study. EGFR mutation status in exons 18-21 of the tyrosine kinase-binding domain was detected using nested PCR amplification of individual exon. The chi (2) test was used to analyze the associations between EGFR mutations and the different variables. The log-rank test and Cox regression model were used to evaluate the factors influencing disease-free survival (DFS) and overall survival (OS). EGFR mutations in 18-21 exons were detected in 58 of the 131 patients (44.3 %). Smoking status (P = 0.029), N stage (P = 0.021), and pathologic stage (P = 0.048) were significantly associated with EGFR mutations. The median DFS in mutant EGFR and wild-type EGFR groups was 36.6 and 25.7 months, respectively (P = 0.533). No significant correlation was observed between EGFR mutations and OS (P = 0.564). However, patients with exon 19 mutation tended to have longer DFS than those with exon 21 mutation (46.2 vs. 21.9 months, P = 0.056), and the 1-, 2-, and 3-year OS rates were significantly higher in patients with exon 19 mutation compared to patients with exon 21 mutation (100, 96.7, 93.3 vs. 91.3, 82.6, 60.9 %, respectively, P = 0.01). Our data demonstrated that EGFR mutations do not have significant prognostic value in primary resected lung adenocarcinomas, but patients with exon 19 mutation tended to have better prognostic value compared to patients with exon 21 mutation.

[558]

**TÍTULO / TITLE:** - Targeting Apoptosis Pathways for New Cancer Therapeutics.

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

**REVISTA / JOURNAL:** - Annu Rev Med. 2013 Nov 4.

●● Enlace al texto completo (gratis o de pago) [1146/annurev-med-010713-141310](#)

**AUTORES / AUTHORS:** - Bai L; Wang S

**INSTITUCIÓN / INSTITUTION:** - University of Michigan Comprehensive Cancer Center and Departments of Internal Medicine, Pharmacology, and Medicinal Chemistry, University of Michigan, Ann Arbor, MI 48109.

**RESUMEN / SUMMARY:** - The past decade has witnessed tremendous advances in the discovery and development of novel small-molecule inhibitors targeting apoptosis pathways for cancer treatment, with some compounds now in clinical development. Early promising clinical data have been reported with these new classes of anticancer drugs. This review highlights the recent advancements in the development of small-molecule inhibitors targeting three major classes of antiapoptotic proteins: antiapoptotic B cell lymphoma 2 (BCL-2) proteins, inhibitor of apoptosis proteins (IAPs), and murine double-minute 2 (MDM2). Special emphasis is given to those that have been advanced into clinical trials. The challenges and future directions in the further preclinical and clinical development of these new anticancer drugs are also discussed. Expected final online publication date for the Annual Review of Medicine Volume 65 is January 14, 2014. Please see <http://www.annualreviews.org/catalog/pubdates.aspx> for revised estimates.

[559]

**TÍTULO / TITLE:** - Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition: Partial mediation by the transcription factor NFAT

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

**REVISTA / JOURNAL:** - Mol Carcinog. 2013 Nov 14. doi: 10.1002/mc.22100.

●● Enlace al texto completo (gratis o de pago) [1002/mc.22100](#)

**AUTORES / AUTHORS:** - Dai W; Wang F; He L; Lin C; Wu S; Chen P; Zhang Y; Shen M; Wu D; Wang C; Lu J; Zhou Y; Xu X; Xu L; Guo C

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University, School of Medicine, Shanghai, China.

**RESUMEN / SUMMARY:** - To investigate the effects and mechanism of genistein on hepatocellular carcinoma. Cell counting kit-8 assays showed that genistein at 3, 6, and 9 microM had no significant cytotoxic effects on HepG2, SMMC-7721, and Bel-7402 cells. Cell scratch and Transwell assays identified that genistein inhibited migration of three cell lines. In three cell lines, genistein enhanced E-cadherin and alpha-catenin, but reduced N-cadherin and Vimentin at both mRNA and protein levels in a dose-dependent manner. Simultaneously, treatment with genistein suppressed epithelial-mesenchymal transition (EMT) induced by TGF-beta. In HepG2 cells, genistein reduced mRNA, and protein expressions of nuclear factor of activated T cells 1 (NFAT1), Abca3, Autotaxin, CD154, and Cox-2. Phorbol 12-myristate 13-acetate (PMA) and ionomycin enhanced activity of NFAT1, reduced E-cadherin and alpha-catenin protein levels, and increased protein levels of N-cadherin and Vimentin. Transwell demonstrated that PMA and ionomycin reversed the migration inhibitory effects of genistein on HepG2 cells. In vivo, genistein inhibited the intrahepatic metastasis by

reversing the EMT, which was correlated with reduced NFAT1 . Genistein inhibited hepatocellular carcinoma cell migration by reversing the EMT, which was partly mediated by NFAT1 . The fact that EMT can be reversed by genistein may shed light on the possible mechanisms for its role in liver cancer therapy. © 2013 Wiley Periodicals, Inc.

[560]

**TÍTULO / TITLE:** - Purification and Characterization of a Glucosamine-Binding Antifungal Lectin from Phaseolus vulgaris cv. Chinese Pinto Beans with Antiproliferative Activity Towards Nasopharyngeal Carcinoma Cells.

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

**REVISTA / JOURNAL:** - Appl Biochem Biotechnol. 2013 Oct 10.

●● Enlace al texto completo (gratis o de pago) [1007/s12010-013-0542-2](#)

**AUTORES / AUTHORS:** - Ang AS; Cheung RC; Dan X; Chan YS; Pan W; Ng TB

**INSTITUCIÓN / INSTITUTION:** - Faculty of Science, School of Life Sciences, The Chinese University of Hong Kong, Hong Kong, China.

**RESUMEN / SUMMARY:** - A lectin has successfully been isolated from Phaseolus vulgaris cv. Chinese pinto bean using affinity chromatography, ion exchange chromatography, and gel filtration in succession, with a 15.4-fold purification. Investigation of its characteristics revealed that Chinese pinto bean lectin (CPBL) was a 58-kDa dimeric glucosamine-binding protein. Its Mg<sup>2+</sup>-dependent hemagglutinating activity was stable at pH 7-8 and at or below 60 degrees C. When the purified lectin was tested against six fungal species including Phyllosticta citriasiana, Magnaporthe grisea, Bipolaris maydis, Valsa mali, Mycosphaerella arachidicola, and Setosphaeria turcica, only the mycelial growth of V. mali was reduced by 30.6 % by the lectin at 30 μM. The lectin did not exert any discernible antiproliferative effects on breast cancer MCF-7 cells, but was able to suppress proliferation of nasopharyngeal carcinoma HONE-1 cells, with an IC<sub>50</sub> of 17.3 μM, as revealed by the MTT assay. Since few plant lectins demonstrate antifungal activity against V. mali, and not many others have inhibitory effects on HONE-1 cells, CPBL is a distinctive lectin which may be exploited for development into an agent against V. mali and HONE-1 cells.

[561]

**TÍTULO / TITLE:** - Biodegradable self-assembled nanoparticles of poly (d,l-lactide-co-glycolide)/hyaluronic acid block copolymers for target delivery of docetaxel to breast cancer.

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

**REVISTA / JOURNAL:** - Biomaterials. 2014 Jan;35(1):550-66. doi: 10.1016/j.biomaterials.2013.09.089. Epub 2013 Oct 15.

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

[1016/j.biomaterials.2013.09.089](#)

**AUTORES / AUTHORS:** - Huang J; Zhang H; Yu Y; Chen Y; Wang D; Zhang G; Zhou G; Liu J; Sun Z; Sun D; Lu Y; Zhong Y

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutical Science, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, China.

**RESUMEN / SUMMARY:** - To develop biodegradable docetaxel-loaded self-assembled nanoparticles of poly (d,l-lactide-co-glycolide)/hyaluronic acid block copolymers were successfully synthesized. These copolymers could form nanoparticles with small size (<200 nm), an acceptable CMC ( approximately 7.9 mg/L), typical core/shell structure and superior stability in one week. DTX-loaded PLGA502H-b-HA5.6k nanoparticles (DTX/SANPs) showed a biphasic release pattern within 120 h, and exhibited enhanced cytotoxicity toward CD44-overexpressing MDA-MB-231 cells. Cellular uptake study indicated that PLGA502H-b-HA5.6k nanoparticles (SANPs) were taken up in MDA-MB-231 cells by CD44-mediated endocytosis. Pharmacokinetics study revealed DTX/SANPs could prolong the circulation of DTX in the blood. In vivo studies demonstrated that SANPs exhibited enhanced tumor targeting and antitumor activity with lower systemic toxicity. In conclusion, DTX/SANPs have great potential for targeted chemotherapy for CD44-overexpressing breast cancer.

[562]

**TÍTULO / TITLE:** - High fibroblast growth factor 19 (FGF19) expression predicts worse prognosis in invasive ductal carcinoma of breast.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 19.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1374-y](#)

**AUTORES / AUTHORS:** - Buhmeida A; Dallol A; Merdad A; Al-Maghrabi J; Gari MA; Abu-Elmagd MM; Chaudhary AG; Abuzenadah AM; Nedjadi T; Ermiah E; Al-Thubaity F; Al-Qahtani MH

**INSTITUCIÓN / INSTITUTION:** - Center of Excellence in Genomic Medicine Research, King Abdulaziz University, P.O. Box 80216, Jeddah, 21589, Kingdom of Saudi Arabia.

**RESUMEN / SUMMARY:** - Metabolic diseases like diabetes and obesity are major risk factors for breast cancer. Aberrant expression of metabolic effectors such as fibroblast growth factor 19 (FGF19) could be therefore associated with the disease. The expression of FGF19 was examined in 193 archival breast tumor samples by immunohistochemistry and evaluated semi-quantitatively by determining the staining index and correlating it with clinicopathological parameters using Fisher's exact test. The correlation between FGF19 expression and 5-year disease-specific survival rate was determined using the univariate Kaplan-Meier analysis. The prognostic value of FGF19 expression was evaluated using the multivariate Cox regression analysis. Of the 193 tumors analyzed, 40 % were classified with low FGF19 expression, whereas 60 % were categorized as tumors with high FGF19 expression. There was a highly significant correlation between high FGF19 expression and patients' age ( $p = 0.008$ ) as well as 5-year disease-specific survival ( $p = 0.001$ ). However, FGF19 expression did not show any significant correlations with other clinicopathological parameters, including hormonal status, tumor grade, tumor size, or lymph node status. Univariate Kaplan-Meier log rank analysis showed that patients with high FGF19 expression exhibited a significantly shorter disease-specific 5-year survival ( $p = 0.007$ ). This effect was exacerbated by lymph node metastasis ( $p = 0.001$ ), negative estrogen receptor (ER) status ( $p = 0.002$ ), or old age ( $p = 0.013$ ). Multivariate analysis showed that high FGF19 expression could be an independent prognostic marker of disease-specific survival in breast cancer patients ( $p = 0.030$ ). Quantification of FGF19 expression

appears to provide valuable prognostic information in breast cancer, particularly in older patients with lymph node metastasis and negative ER status.

[563]

**TÍTULO / TITLE:** - Developing Biomarkers to Predict Benefit from HGF/MET Pathway Inhibitors.

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

**REVISTA / JOURNAL:** - J Pathol. 2013 Sep 19. doi: 10.1002/path.4268.

●● [Enlace al texto completo \(gratis o de pago\) 1002/path.4268](#)

**AUTORES / AUTHORS:** - Koeppen H; Rost S; Yauch RL

**INSTITUCIÓN / INSTITUTION:** - Departments of Research Pathology and Discovery Oncology, Genentech, Inc., South San Francisco, CA.

**RESUMEN / SUMMARY:** - Activation of the MET signaling pathway is critical in regulating multiple cellular processes underlying tumorigenic growth and has represented an attractive target for therapeutic intervention in cancer. Early stage clinical studies of multiple agents targeting this pathway have been undertaken, frequently in unselected patient cohorts with variable results. Promising data in patient subgroups in these studies indicate the need for predictive biomarkers to identify the patients most likely to benefit from these therapies. In this review, we discuss the current knowledge of mechanisms of MET activation, the status of the clinical evaluation of MET-targeted therapies, the associated efforts to identify and validate biomarkers and the considerations and challenges for potential development of companion diagnostics.

[564]

**TÍTULO / TITLE:** - Pro-apoptotic TP53 homolog TAp63 is repressed via epigenetic silencing and B-cell receptor signalling in chronic lymphocytic leukaemia.

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

**REVISTA / JOURNAL:** - Br J Haematol. 2013 Dec;163(5):590-602. doi: 10.1111/bjh.12580. Epub 2013 Sep 30.

●● [Enlace al texto completo \(gratis o de pago\) 1111/bjh.12580](#)

**AUTORES / AUTHORS:** - Humphries LA; Godbersen JC; Danilova OV; Kaur P; Christensen BC; Danilov AV

**INSTITUCIÓN / INSTITUTION:** - Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA.

**RESUMEN / SUMMARY:** - Chronic lymphocytic leukaemia (CLL) is an accumulative disorder marked by deficient apoptosis. The TP53 homolog TAp63 promotes apoptosis and chemosensitivity in solid tumours and its deregulation may contribute to CLL cell survival. We found that TAp63alpha was the most prevalent TP63 isoform in CLL. Compared to healthy B cells, TAp63 mRNA was repressed in 55.7% of CLL samples. TP63 promoter methylation was high in CLL and inversely correlated with TP63 protein expression in B-cell lymphoma cell lines. siRNA-mediated knockdown of TP63 resulted in partial protection from spontaneous apoptosis accompanied by reductions in PMAIP1 (NOXA), BBC3 (PUMA), and BAX mRNA in CLL cells and increased proliferation of Raji lymphoma cells. TAp63 mRNA levels were higher in CLL with unmutated IGHV. B-cell receptor (BCR) engagement led to repression of TP63 mRNA

expression in malignant B cells, while pharmacological inhibition of BCR signalling prevented TP63 downregulation. MIR21, known to target TAp63, correlated inversely with TAp63 expression in CLL, and BCR-mediated downregulation of TP63 was accompanied by MIR21 upregulation in most CLL samples. Our data illustrate the pro-apoptotic function of TP63, provide insights into the mechanisms of BCR-targeting agents, and establish a rationale for designing novel approaches to induce TP63 in CLL and B-cell lymphoma.

[565]

**TÍTULO / TITLE:** - Telomere length, c-myc and mad-1 expression could represent prognosis markers of myelodysplastic syndrome.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Nov;37(11):1538-44. doi: 10.1016/j.leukres.2013.07.022. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.07.022](#)

**AUTORES / AUTHORS:** - Poloni A; Serrani F; Berardinelli E; Maurizi G; Mariani M; Costantini B; Trappolini S; Mancini S; Olivieri A; Leoni P

**INSTITUCIÓN / INSTITUTION:** - Clinica di Ematologia, Dipartimento Scienze Cliniche e Molecolari, Ancona, Italy. Electronic address: [a.poloni@univpm.it](mailto:a.poloni@univpm.it).

**RESUMEN / SUMMARY:** - Telomere dysfunction might generate genomic instability leading to the progression of myelodysplastic syndromes (MDS) into acute myeloid leukemia (AML). We investigated telomere length (TL), telomerase activity (TA) and hTERT, c-myc, mad1, and p53 expression in the bone marrow of patients with MDS (n=109), AML (n=47) and in controls (n=24). TL was lower in MDS patients than in controls (p<0.001) and higher in L-MDS (low, intermediate-1 IPSS, p<0.01) respect H-MDS (high, intermediate-2 IPSS, p<0.01) patients. Mad-1 expression was higher in MDS patients than in controls (p<0.01), c-myc expression was highest in AML and in H-MDS patients. Our results show that the telomere dynamics might be useful for stratifying patients according to a risk scoring system.

[566]

**TÍTULO / TITLE:** - Histone deacetylase inhibitors: an overview of the clinical studies in solid tumors.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Oct 31.

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

[1097/CAD.0000000000000040](#)

**AUTORES / AUTHORS:** - Slingerland M; Guchelaar HJ; Gelderblom H

**INSTITUCIÓN / INSTITUTION:** - Departments of aClinical Oncology bClinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.

**RESUMEN / SUMMARY:** - The histone deacetylase inhibitors (HDACi) are a group of small molecules that target histone deacetylases (HDACs) by inhibiting their activity. HDACi have a long history of use in neurology and psychiatry as antiepileptics and mood stabilizers. More recently, they have been investigated as possible treatments for cancer. HDACi have undergone rapid clinical development in recent years, on the basis of their preclinical in-vitro and in-vivo antitumor activity in hematological

malignancies and solid tumors. Many HDACi have entered phase I-III clinical trials. Among the HDACi, vorinostat and romidepsin are currently the most extensively studied. In 2006 and 2009, respectively, they received approval by the United States Food and Drug Administration for treatment of cutaneous T-cell lymphoma and romidepsin for the treatment of peripheral T-cell lymphoma. Other HDACi, such as panobinostat and valproic acid, also demonstrated activity as therapeutic anticancer agents. In this article we give an overview of the clinical studies of HDACi in solid tumors. We start with a short description of the working mechanism of HDACi in general.

[567]

**TÍTULO / TITLE:** - Effect of combined treatment with recombinant interleukin-2 and allicin on pancreatic cancer.

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

**REVISTA / JOURNAL:** - Mol Biol Rep. 2013 Dec;40(12):6579-85. doi: 10.1007/s11033-013-2766-1. Epub 2013 Oct 18.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11033-013-2766-1](#)

**AUTORES / AUTHORS:** - Wang CJ; Wang C; Han J; Wang YK; Tang L; Shen DW; Zhao Y; Xu RH; Zhang H

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Shanghai East Hospital, Tongji University School of Medicine, No.150 Jimo Road, Pudong New District, Shanghai, 200120, China.

**RESUMEN / SUMMARY:** - This study aimed to evaluate the efficacy of combined treatment with recombinant interleukin-2 (rIL-2) and allicin on pancreatic cancer and explore the potential immunological mechanism. A total of 60 C57/BL6 nude mice pancreatic cancer xenograft models were randomized into four groups of 15 mice per group: control group, allicin treatment group, rIL-2 treatment group, combined treatment with allicin and rIL-2 group. Mice in each group were treated with saline, rIL-2, allicin, or combination of rIL-2 and allicin by weekly i.v injection for four weeks. After four weeks of treatment, eyeballs of the mice were extracted and blood was drawn, percentages of CD4+T, CD8+T and NK cell were analyzed by FACS, IFN-gamma level was detected by ELISA. One mouse in each group was sacrificed to measure the weight and volume of the tumor and prepared to the paraffin section of tumor tissue. Apoptosis of the tumor cells was analyzed by TUNEL and FACS. Other mice continued to receive treatment, survival period were compared between each group. We observed a significant suppression of xenograft growth and a significant prolonged survival time in the combined treatment with allicin and rIL-2 group ( $P < 0.05$ ). The most amount of apoptotic cells were observed in the combined therapy group ( $P < 0.05$ ). The percentages of CD4+T, CD8+T and NK cell and serum IFN-gamma level increased significantly in the combined treatment group compared with other groups ( $P < 0.05$ ). Combined treatment with allicin and rIL-2 resulted in suppression of tumor growth and prolonged survival time possibly through activation of CD4+T, CD8+T and NK cell.

[568]

**TÍTULO / TITLE:** - Second hepatectomy for recurrent hepatocellular carcinoma achieved sustained virological response to interferon therapy for hepatitis C.

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

**REVISTA / JOURNAL:** - Hepatogastroenterology. 2013 Oct 2;60(128). doi: 10.5754/hge13382.

●● Enlace al texto completo (gratis o de pago) [5754/hge13382](#)

**AUTORES / AUTHORS:** - Tsujita E; Yamashita YI; Takeishi K; Maeda T; Takaki SI; Mori N; Aisaka Y; Furukawa Y; Shirabe K; Ishida T; Maehara Y

**RESUMEN / SUMMARY:** - Background/Aims: Interferon (IFN) improves the prognosis of HCV-related hepatocellular carcinoma (HCC) in patients. However, the effects of IFN therapy for second hepatectomy (Hx) for recurrent HCC have not been established. Methodology: Subjects included 96 patients who underwent a second Hx for recurrence of HCV-related HCC. Forty-four patients received IFN therapy past or postoperatively of the first Hx. Twenty of those patients attained a sustained viral response (SVR). The other 24 were non-responders (NR) and 52 patients who had not received IFN therapy (non-IFN) were classified as the NR/non-IFN group. Results: Overall survival (SVR group vs. NR/non-IFN group: 5-yr, 91.7 vs. 51.0%;  $p = 0.012$ ) and disease-free survival (SVR group vs. NR/non-IFN group: 3-yr, 64.7 vs. 25.9%;  $p = 0.006$ ) rates were significantly different in both groups. By multivariate analysis, NR/non-IFN therapy, was the independent risk factor for overall survival ( $p = 0.025$ ) and disease-free survival ( $p = 0.006$ ) after second Hx. Conclusions: SVR achieved past or postoperatively of the first Hx of HCV-related HCC significantly inhibits recurrence and consequently improves patient survival after second Hx for recurrent HCC. Patients with SVR to IFN therapy would be good candidates for second Hx for recurrent HCC.

[569]

**TÍTULO / TITLE:** - Musashi2 modulates K562 leukemic cell proliferation and apoptosis involving the MAPK pathway.

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

**REVISTA / JOURNAL:** - Exp Cell Res. 2014 Jan 1;320(1):119-27. doi: 10.1016/j.yexcr.2013.09.009. Epub 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1016/j.yexcr.2013.09.009](#)

**AUTORES / AUTHORS:** - Zhang H; Tan S; Wang J; Chen S; Quan J; Xian J; Zhang SS; He J; Zhang L

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Laboratory Medical Diagnostics Designated by the Ministry of Education, College of Laboratory Medicine, Chongqing Medical University, 1#, Yixueyuan Road, Chongqing 400016, China.

**RESUMEN / SUMMARY:** - The RNA-binding protein Musashi2 (Msi2) has been identified as a master regulator within a variety of stem cell populations via the regulation of translational gene expression. A recent study has suggested that Msi2 is strongly expressed in leukemic cells of acute myeloid leukemia patients, and elevated Msi2 is associated with poor prognosis. However, the potential role of Msi2 in leukemogenesis is still not well understood. Here, we investigated the effect of Msi2 knockdown on the biological properties of leukemic cells. High expression of Msi2 was found in K562 and KG-1a leukemic cell lines, and low expression was observed in the U937 cell line. We transduced K562 cells with two independent adenoviral shRNA

vectors targeting Msi2 and confirmed knockdown of Msi2 at the mRNA and protein levels. Msi2 silencing inhibited cell growth and caused cell cycle arrest by increasing the expression of p21 and decreasing the expression of cyclin D1 and cdk2. In addition, knockdown of Msi2 promoted cellular apoptosis via the upregulation of Bax and downregulation of Bcl-2 expression. Furthermore, Msi2 knockdown resulted in the inactivation of the ERK/MAPK and p38/MAPK pathways, but no remarkable change in p-AKT was observed. These data provide evidence that Msi2 plays an important role in leukemogenesis involving the MAPK signaling pathway, which indicates that Msi2 may be a novel target for leukemia treatment.

[570]

**TÍTULO / TITLE:** - Molecular Mechanisms of Hepatocellular Apoptosis Induced by Trovafloxacin-Tumor Necrosis Factor-alpha Interaction.

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

**REVISTA / JOURNAL:** - Toxicol Sci. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1093/toxsci/kft226](#)

**AUTORES / AUTHORS:** - Beggs KM; Fullerton AM; Miyakawa K; Ganey PE; Roth RA

**INSTITUCIÓN / INSTITUTION:** - \* Department of Pharmacology & Toxicology and.

**RESUMEN / SUMMARY:** - Idiosyncratic drug-induced liver injury (IDILI) continues to be a significant human health problem. IDILI is characterized as occurring in a minority of individuals exposed to a drug, yet it accounts for as much as 17% of all cases of acute liver failure. Despite these concerns, the mechanisms underlying IDILI remain unknown. Trovafloxacin (TVX), which causes IDILI in humans, also causes hepatocellular death in vitro when combined with tumor necrosis factor-alpha (TNF) treatment. However, the molecular mechanisms involved in this toxicity are not fully characterized. The purpose of this study was to identify mechanisms by which TVX and TNF interact to cause hepatocellular death, with a focus on a human hepatocyte cell line. TVX and TNF interacted to cause cytotoxicity in HepG2 cells at drug concentrations similar to those in people undergoing TVX therapy. TVX/TNF treatment caused apoptosis and DNA damage in HepG2 cells that depended on caspase activation. Prolonged activation of JNK occurred in TVX/TNF-induced cytotoxicity, and treatment with the JNK selective inhibitor SP600125 attenuated cytotoxicity. TVX/TNF cotreatment also caused cytotoxicity in isolated primary murine hepatocytes that was dependent on caspase activation. These results increase understanding of molecular signaling pathways involved in hepatocellular death caused by a drug with idiosyncratic liability in the presence of TNF.

[571]

**TÍTULO / TITLE:** - MicroRNAs with Prognostic Potential for Metastasis in Clear Cell Renal Cell Carcinoma: A Comparison of Primary Tumors and Distant Metastases.

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

**REVISTA / JOURNAL:** - Ann Surg Oncol. 2013 Nov 18.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3361-3](#)

**AUTORES / AUTHORS:** - Heinzelmann J; Unrein A; Wickmann U; Baumgart S; Stapf M; Szendroi A; Grimm MO; Gajda MR; Wunderlich H; Junker K

**INSTITUCIÓN / INSTITUTION:** - Clinic of Urology and Pediatric Urology, Saarland University Medical Center, Homburg/Saar, Germany, [joana.heinzelmann@uks.eu](mailto:joana.heinzelmann@uks.eu).

**RESUMEN / SUMMARY:** - BACKGROUND: MicroRNAs (miRNAs) are regulators of gene expression in tumor development and progression. However, their influence on metastasis of clear cell renal cell carcinoma (ccRCC) is less understood. To determine the role of miRNAs in metastatic progression, miRNA expression in primary ccRCC was compared to distant metastases. METHODS: Total RNA of 53 primary ccRCCs, 35 distant metastases from lung, bone, brain, and abdomen, as well as 17 normal kidney tissues was isolated from fresh frozen tissue and formalin-fixed paraffin-embedded (FFPE) samples. The miRNA microarrays were performed based on fresh frozen tissue. Results were validated by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) on fresh frozen tissue and FFPE samples. Real-time cell analyses and transwell invasion assays were carried out after transient transfection of microRNA-30c (miR-30c) in cell line 786-O. RESULTS: There were 14 miRNAs differently expressed in metastatic primary ccRCC and distant metastases compared to non-metastatic primary tumors. A strong correlation of miRNAs to progression-free- and cancer-specific 5-year-survival was determined. Specific miRNAs were differently expressed in distant metastases compared to primary ccRCC. A miRNA signature distinguished lung metastases from other metastatic sites. Overexpression of miR-30c increased adherence and decreased migration and invasion in the ccRCC cell line. CONCLUSIONS: MiRNAs are deregulated in metastatic primary ccRCC and could be promising prognostic markers for an early prediction of metastasis. Alterations in miRNA expression characterize distant metastases of different metastatic sites. Furthermore, our study suggests a functional role of miR-30c in metastasis. The miRNAs could be a helpful tool for individual follow-up prediction and personalized therapy selection.

[572]

**TÍTULO / TITLE:** - High-Dose Eicosapentaenoic Acid and Docosahexaenoic Acid Supplementation Reduces Bone Resorption in Postmenopausal Breast Cancer Survivors on Aromatase Inhibitors: A Pilot Study.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Nov 25.

●● [Enlace al texto completo \(gratis o de pago\) 1080/01635581.2014.847964](#)

**AUTORES / AUTHORS:** - Hutchins-Wiese HL; Picho K; Watkins BA; Li Y; Tannenbaum S; Claffey K; Kenny AM

**INSTITUCIÓN / INSTITUTION:** - a Eastern Michigan University, Dietetics and Human Nutrition, Ypsilanti, Michigan, USA, and Center on Aging, University of Connecticut, Farmington, Connecticut, USA.

**RESUMEN / SUMMARY:** - Postmenopausal breast cancer survivors are living longer; however, a common class of drugs, aromatase inhibitors (AI), depletes estrogen levels, promotes bone loss, and heightens fracture risk. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may offset AI effects to bone because of the known effects on cellular processes of bone turnover. Therefore, we hypothesized that 4 g of EPA and DHA daily for 3 mo would decrease bone turnover in postmenopausal breast cancer survivors on AI therapy in a randomized, double-blind, placebo controlled pilot study that included 38 women. At baseline and 3 mo, serum fatty acids, bone turnover,

and inflammatory markers were analyzed. Serum EPA and DHA, total and long-chain (LC) omega (n)-3 polyunsaturated fatty acids (PUFA) increased, whereas arachidonic acid, total and LC n-6 PUFA, and the LC n-6:n-3 PUFA ratio decreased compared to placebo (all  $P < .05$ ). Bone resorption was inhibited in the fish oil responders compared to placebo ( $P < .05$ ). Inflammatory markers were not altered. This short-term, high-dose fish oil supplementation study's findings demonstrate that fish oil can reduce bone resorption; however, longer-term studies are needed to assess bone density preservation and to explore mechanistic pathways in this population at high risk for bone loss.

[573]

**TÍTULO / TITLE:** - Combretastatin A-4 induces p53 mitochondrial-relocalisation independent-apoptosis in non-small lung cancer cells.

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

**REVISTA / JOURNAL:** - Cell Biol Int. 2013 Oct 23. doi: 10.1002/cbin.10199.

●● Enlace al texto completo (gratis o de pago) [1002/cbin.10199](#)

**AUTORES / AUTHORS:** - Mendez-Callejas GM; Leone S; Tanzarella C; Antoccia A

**INSTITUCIÓN / INSTITUTION:** - Departament of Science University 'Roma Tre', V.le G. Marconi 446, 00146, Rome, Italy; Universidad de Ciencias Aplicadas y Ambientales, Calle 222, 55-37, Bogota, Colombia.

**RESUMEN / SUMMARY:** - Combretastatin A-4 (CA-4) is one of the most effective agents used in chemotherapy. Nevertheless, the contribution of p53 and Bim proteins in the CA-4-induced apoptosis in non-small lung cancer cells (NSCLC) remains unresolved, specifically on involving of p53 in the mitochondrial pathway activation by a transcription-independent mechanism. In this context, the p53-null H1299 and wt-p53 H460 NSCLC cells, in the absence and presence of pifithrin-micro (PFTmicro), an inhibitor of p53 mitochondrial-translocation, were treated with CA-4 and different cellular endpoints were analysed. In contrast to previous observations in H460 cells, CA-4 failed in the activation of an apoptotic response in H1299 cells, thus indicating an involvement of p53 in the cell death induced by the drug. We found that CA-4 led to p53 cellular re-localisation in H460 cells; in particular, p53 was released from the microtubular network and accumulated at mitochondria where it interacts with Bim protein and other proteins of the Bcl-2 (B-cell leukaemia-2) family, leading to cytochrome c release, alteration in the mitochondrial membrane polarisation, cell cycle arrest at the G2/M-phase, and cell death. Interestingly, the cytosolic and the mitochondrial accumulation of protein Bim was strictly dependent on p53 status. The extent of cell death was not reduced in H460 after combined treatment of PFTmicro with CA-4. Overall, the data support a model of CA-4-induced apoptosis in NSCLC, for which the expression of p53 protein is essential, but its mitochondrial function, linked to p53-transcription independent apoptosis pathway, is negligible.

[574]

**TÍTULO / TITLE:** - The mTOR effectors 4EBP1 and S6K2 are frequently coexpressed, and associated with a poor prognosis and endocrine resistance in breast cancer: a retrospective study including patients from the randomised Stockholm tamoxifen trials.

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

**REVISTA / JOURNAL:** - Breast Cancer Res. 2013 Oct 17;15(5):R96.

●● Enlace al texto completo (gratis o de pago) [1186/bcr3557](http://1186/bcr3557)

**AUTORES / AUTHORS:** - Karlsson E; Perez-Tenorio G; Amin R; Bostner J; Skoog L; Fornander T; Sgroi DC; Nordenskjold B; Hallbeck AL; Stal O

**RESUMEN / SUMMARY:** - INTRODUCTION: mTOR and its downstream effectors the 4E-binding protein 1 (4EBP1) and the p70 ribosomal S6 kinases (S6K1 and S6K2) are frequently upregulated in breast cancer, and assumed to be driving forces in tumorigenesis, in close connection with oestrogen receptor (ER) networks. Here, we investigated these factors as clinical markers in five different cohorts of breast cancer patients. METHODS: The prognostic significance of 4EBP1, S6K1 and S6K2 mRNA expression was assessed with real-time PCR in 93 tumours from the treatment randomised Stockholm trials, encompassing postmenopausal patients enrolled between 1976 and 1990. Three publicly available breast cancer cohorts were used to confirm the results. Furthermore, the predictive values of 4EBP1 and p4EBP1\_S65 protein expression for both prognosis and endocrine treatment benefit were assessed by immunohistochemical analysis of 912 node-negative breast cancers from the Stockholm trials. RESULTS: S6K2 and 4EBP1 mRNA expression levels showed significant correlation and were associated with a poor outcome in all cohorts investigated. 4EBP1 protein was confirmed as an independent prognostic factor, especially in progesterone receptor (PgR)-expressing cancers. 4EBP1 protein expression was also associated with a poor response to endocrine treatment in the ER/PgR positive group. Cross-talk to genomic as well as non-genomic ER/PgR signalling may be involved and the results further support a combination of ER and mTOR signalling targeted therapies. CONCLUSION: This study suggests S6K2 and 4EBP1 as important factors for breast tumorigenesis, interplaying with hormone receptor signalling. We propose S6K2 and 4EBP1 as new potential clinical markers for prognosis and endocrine therapy response in breast cancer.

[575]

**TÍTULO / TITLE:** - Wilms' tumor gene 1 enhances nutlin-3-induced apoptosis.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):131-6. doi: 10.3892/or.2013.2832. Epub 2013 Nov 1.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2832](http://3892/or.2013.2832)

**AUTORES / AUTHORS:** - Lee SY; Choe YJ; Park JY; Lee SS; Kim YH; Shin SJ; Chung YJ; Kim HS

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, College of Medicine, The Catholic University of Korea, Seoul 137-701, Republic of Korea.

**RESUMEN / SUMMARY:** - Nutlin-3, a human double minute 2 (HDM2) antagonist, induces cell cycle arrest or apoptosis by upregulating p53 in cancer cells. WT1, the product of Wilms' tumor gene 1, has been shown to interact with p53, but the effect of WT1 on nutlin-3-induced apoptosis has yet to be examined. To address this issue, we analyzed the inhibitory effect of nutlin-3 on cell growth as a function of Wt1 expression status using a Wt1-inducible U2OS cell line. In the absence of Wt1 expression, nutlin-3 induced cell cycle arrest with marginal cytotoxicity. Furthermore, upon Wt1 expression, nutlin-3 exerted a marked degree of cell death, as evidenced by the accumulation of hypo-diploid cells and LDH release. During cell death induction, cytochrome c was

released into the cytosol, and caspase-9 and -3 were activated, suggesting that an intrinsic apoptotic pathway may be involved in this cell death. Consistent with this, z-VAD-Fmk, a pan-caspase inhibitor and the overexpression of BCL-XL attenuated the cell death. Nutlin-3 caused an increase in the mRNA levels of both BCL-XL and BAK, as well as their corresponding protein levels in mitochondria. In the presence of Wt1, nutlin-3-induced BCL-XL expression was attenuated while the expression of nutlin-3-induced BAK was potentiated. Collectively, these results suggest that WT1 potentiates nutlin-3-induced apoptosis by downregulating the expression of BCL-XL while upregulating that of BAK, which leads to the activation of an intrinsic apoptotic pathway.

[576]

**TÍTULO / TITLE:** - WW domain containing oxidoreductase induces apoptosis in gallbladder-derived malignant cell by upregulating expression of P73 and PUMA.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 15.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1213-1](#)

**AUTORES / AUTHORS:** - Wei D; Zhang X; Zou H; Wang L; Fu B; Wu X; Luo Z; Li X; Ge J; Li Y; Zhu H; Wang K; Wang T; Yang P; Hou Z; Wang W

**INSTITUCIÓN / INSTITUTION:** - Department of Hepatopancreatobiliary Surgery, The Second Affiliated Hospital of Kunming Medical University, Kunming, 650101, Yunnan, People's Republic of China.

**RESUMEN / SUMMARY:** - Gallbladder cancer (GBC) is one leading cause of cancer-related death worldwide. WW domain-containing oxidoreductase (WWOX) is a tumor suppressor gene which can suppress proliferation of a variety of tumors. However, little was known about the relationships between WWOX and gallbladder cancer. In the current study, we intended to investigate the tumor suppressive role of WWOX in gallbladder malignant cells both in vitro and in vivo, and explore the potential mechanism of tumor toxic function of WWOX. Our results have shown that WWOX triggered apoptosis in GBC cells and increased the expression of P73 and PUMA in cytoplasm. We also have found that Bax has been upregulated after overexpression of WWOX, whereas, Bcl-2 was downregulated by WWOX. To further validate the results in vivo, we evaluated the tumor suppressive role of WWOX in mouse model of gallbladder cancer. The results have shown that the proliferation of the tumor was inhibited after delivery of WWOX, and the expressions of P73 and PUMA were upregulated in target tissues. The mice models administrated with WWOX have shown better prognosis than mice in negative control groups. The results from our study indicated that WWOX could be used as a therapeutic agent in the gene therapy of gallbladder cancer.

[577]

**TÍTULO / TITLE:** - Up-regulation of tripartite motif-containing 29 promotes cancer cell proliferation and predicts poor survival in colorectal cancer.

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

**REVISTA / JOURNAL:** - Med Oncol. 2013 Dec;30(4):715. doi: 10.1007/s12032-013-0715-4. Epub 2013 Sep 28.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0715-4](http://1007/s12032-013-0715-4)

**AUTORES / AUTHORS:** - Jiang T; Tang HM; Lu S; Yan DW; Yang YX; Peng ZH

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Shanghai Jiao Tong University Affiliated First People's Hospital, 85 Wujin Road, Shanghai, 200080, People's Republic of China.

**RESUMEN / SUMMARY:** - Tripartite motif-containing 29 (TRIM29), also known as ataxia-telangiectasia group D, is structurally a member of the tripartite motif family of proteins, which characterized by the conserved RING finger, B-box, and coiled-coil domains. TRIM29 functions as an oncogene or a tumor suppressor depending on the tumor types. In this study, we aim to evaluate whether TRIM29 affects the tumorigenesis and progression of colorectal cancer. The expression of TRIM29 was investigated using real-time PCR in 40 pairs of colorectal cancer tissues and immunohistochemistry on a tissue microarray containing 203 cases of primary colorectal cancer paired with non-cancerous tissues. Down-regulation of TRIM29 was achieved by transient transfection in RKO cell lines, and the effects of TRIM29 on tumor proliferation were evaluated by MTT and plate colony formation assays. Results indicated that TRIM29 expression was much higher in colorectal cancer tissues and significantly associated with the depth of tumor invasion, lymph node metastasis, distant metastasis, histological differentiation, vascular invasion, ki-67 index, and advanced tumor stage. Patients with TRIM29-positive tumors had a higher recurrence rate and poorer survival than patients with TRIM29-negative tumors. In multivariate analyses, the TRIM29 expression was an independent factor for determining colorectal cancer prognosis after surgery. Moreover, down-regulation of TRIM29 inhibited tumor cell proliferation in vitro. In conclusion, TRIM29 plays an important role in promoting colorectal cancer progression. Our findings suggest that TRIM29 may serve as a novel biomarker for tumor recurrence and survival for colorectal cancer patients.

[578]

**TÍTULO / TITLE:** - In vitro modulation of MMP-2 and MMP-9 in adult human sarcoma cell lines by cytokines, inducers and inhibitors.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):1787-98. doi: 10.3892/ijo.2013.2113. Epub 2013 Sep 30.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2113](http://3892/ijo.2013.2113)

**AUTORES / AUTHORS:** - Roomi MW; Kalinovsky T; Monterrey J; Rath M; Niedzwiecki A

**INSTITUCIÓN / INSTITUTION:** - Dr. Rath Research Institute, Santa Clara, CA 95050, USA.

**RESUMEN / SUMMARY:** - The highly aggressive adult sarcomas are characterized by high levels of matrix metalloproteinase (MMP)-2 and -9, which play crucial roles in tumor invasion and metastasis by degradation of the extracellular membrane leading to cancer cell spread to distal organs. We examined the effect of cytokines, mitogens, inducers and inhibitors on MMP-2 and MMP-9 secretion in chondrosarcoma (SW-1353), fibrosarcoma (HT-1080), liposarcoma (SW-872) and synovial sarcoma (SW-982) cell lines. The selected compounds included natural cytokines and growth factors, as well as chemical compounds applied in therapy of sarcoma and natural compounds that have demonstrated anticancer therapeutic potential. MMP-2 and MMP-9

secretions were analyzed by gelatinase zymography following 24-h exposure to the tested agents and quantitated by densitometry. Fibrosarcoma, chondrosarcoma, liposarcoma and synovial sarcoma showed bands corresponding to MMP-2 and MMP-9 with dose-dependent enhancement of MMP-9 with phorbol 12-myristate 13-acetate (PMA) treatment. In chondrosarcoma cells, tumor necrosis factor (TNF)-alpha had a stimulatory effect on MMP-9 and insignificant effect on MMP-2 and interleukin (IL)-1beta stimulated MMP-9 and MMP-2. In fibrosarcoma and liposarcoma cells, TNF-alpha had a profound stimulatory effect on MMP-9, but no effect on MMP-2 and in synovial sarcoma an inhibitory effect on MMP-2 and no effect on MMP-9. IL-1beta had a slight inhibitory effect on fibrosarcoma, liposarcoma and synovial sarcoma MMP-2 and MMP-9 except for MMP-9 in synovial sarcoma which showed slight stimulation. Lipopolysaccharide (LPS) stimulated expression of MMP-2 in fibrosarcoma and chondrosarcoma while inhibited it in liposarcoma. Doxycycline, epigallocatechin gallate and the nutrient mixture inhibited MMP-2 and MMP-9 in all cell lines. Actinomycin-D, cyclohexamide, retinoic acid, and dexamethasone inhibited MMP-2 and -9 in chondrosarcoma and fibrosarcoma cells. Our results show that cytokines, mitogens, inducers and inhibitors have an up or down regulatory effect on MMP-2 and MMP-9 expression in adult sarcoma cell lines, suggesting these agents may be effective strategies to treat these cancers.

[579]

**TÍTULO / TITLE:** - Side Effects of Interferon Therapy in Adolescent Melanoma.

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

**REVISTA / JOURNAL:** - *Pediatr Hematol Oncol.* 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [3109/08880018.2013.838725](#)

**AUTORES / AUTHORS:** - Puzik A; Moller J; Meiss F; Kontny U; Rossler J

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Hematology and Oncology, Albert-Ludwigs-University of Freiburg , Mathildenstrasse 1, Freiburg , Germany.

[580]

**TÍTULO / TITLE:** - Granulysin induces apoptotic cell death and cleavage of the autophagy regulator Atg5 in human hematological tumors.

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

**REVISTA / JOURNAL:** - *Biochem Pharmacol.* 2013 Nov 21. pii: S0006-2952(13)00735-1. doi: 10.1016/j.bcp.2013.11.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.11.004](#)

**AUTORES / AUTHORS:** - Aporta A; Catalan E; Galan-Malo P; Ramirez-Labrada A; Perez M; Azaceta G; Palomera L; Naval J; Marzo I; Pardo J; Anel A

**INSTITUCIÓN / INSTITUTION:** - Apoptosis, Immunity & Cancer Group, Dept. Biochemistry and Molecular and Cell Biology, University of Zaragoza and Aragon Health Research Institute (IIS Aragon). Zaragoza. España. Electronic address: [aaporta@unizar.es](mailto:aaporta@unizar.es).

**RESUMEN / SUMMARY:** - Granulysin is a protein present in the granules of human CTL and NK cells, with cytolytic activity against microbes and tumors. Previous work demonstrated that granulysin caused cell death through mitochondrial damage with release of AIF and cytochrome c. However, the molecular mechanism and, especially,

the type of cell death were still not well defined. In the present work we show that granulysin-induced cell death is apoptotic, with phosphatidylserine exposure preceding membrane breakdown and with caspase 3 activation. Granulysin-induced apoptosis is prevented in Jurkat cells over-expressing Bcl-xL or Bcl2, or lacking Bak and Bax or Bim expression, suggesting a central role of the mitochondrial apoptotic pathway. This apoptotic process is initiated by intracellular Ca<sup>2+</sup> increase and mitochondrial ROS generation. We have tested granulysin against other haematological tumor cells such as multiple myeloma cell lines, and cells from B cell chronic lymphocytic leukaemia (B-CLL) patients, finding different degrees of sensitivity. We also show that granulysin induces the cleavage of Atg5 in the complex formed with Atg12, without affecting autophagy. In conclusion, granulysin induces apoptosis on haematological tumor cells and on cells from B-CLL patients, opening the door to research on its use as a new anti-tumoral treatment.

[581]

**TÍTULO / TITLE:** - MiR-34a targets GAS1 to promote cell proliferation and inhibit apoptosis in papillary thyroid carcinoma via PI3K/Akt/Bad pathway.

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

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Nov 29;441(4):958-63. doi: 10.1016/j.bbrc.2013.11.010. Epub 2013 Nov 9.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.11.010](#)

**AUTORES / AUTHORS:** - Ma Y; Qin H; Cui Y

**INSTITUCIÓN / INSTITUTION:** - Department of Fourth Surgery, the Second Affiliated Hospital of Harbin Medical University, 148 Xuefu Road, Nangang District, Harbin 150086, PR China.

**RESUMEN / SUMMARY:** - MicroRNAs (miRNAs) are fundamental regulators of cell proliferation, differentiation, and apoptosis, and are implicated in tumorigenesis of many cancers. MiR-34a is best known as a tumor suppressor through repression of growth factors and oncogenes. Growth arrest specific1 (GAS1) protein is a tumor suppressor that inhibits cancer cell proliferation and induces apoptosis through inhibition of RET receptor tyrosine kinase. Both miR-34a and GAS1 are frequently down-regulated in various tumors. However, it has been reported that while GAS1 is down-regulated in papillary thyroid carcinoma (PTC), miR-34a is up-regulated in this specific type of cancer, although their potential roles in PTC tumorigenesis have not been examined to date. A computational search revealed that miR-34a putatively binds to the 3'-UTR of GAS1 gene. In the present study, we confirmed previous findings that miR-34a is up-regulated and GAS1 down-regulated in PTC tissues. Further studies indicated that GAS1 is directly targeted by miR-34a. Overexpression of miR-34a promoted PTC cell proliferation and colony formation and inhibited apoptosis, whereas knockdown of miR-34a showed the opposite effects. Silencing of GAS1 had similar growth-promoting effects as overexpression of miR-34a. Furthermore, miR-34a overexpression led to activation of PI3K/Akt/Bad signaling pathway in PTC cells, and depletion of Akt reversed the pro-growth, anti-apoptotic effects of miR-34a. Taken together, our results demonstrate that miR-34a regulates GAS1 expression to promote proliferation and suppress apoptosis in PTC cells via PI3K/Akt/Bad pathway. MiR-34a functions as an oncogene in PTC.

[582]

**TÍTULO / TITLE:** - Prognostic value of mitochondrial DNA content and G10398A polymorphism in non-small cell lung cancer.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):3006-12. doi: 10.3892/or.2013.2783. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2783](#)

**AUTORES / AUTHORS:** - Xu H; He W; Jiang HG; Zhao H; Peng XH; Wei YH; Wei JN; Xie CH; Liang C; Zhong YH; Zhang G; Deng D; Zhou YF; Zhou FX

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Hubei Key Laboratory of Tumor Biological Behaviors and Hubei Cancer Clinical Study Center, Wuchang, Wuhan, Hubei 430071, P.R. China.

**RESUMEN / SUMMARY:** - Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortality worldwide. Mitochondrial dysfunction has been postulated to render cancer cells resistant to apoptosis based on the Warburg hypothesis. However, few studies have investigated the prognostic value of mitochondrial DNA (mtDNA) content and G10398A polymorphism in NSCLC patients. mtDNA copy number and G10398A polymorphism in 128 NSCLC tissue samples were assessed by real-time PCR (RT-PCR) and PCR-RFLP respectively, and their relationship to prognosis were analyzed by survival analysis and Cox proportional hazards model. In vitro, an mtDNA deletion A549 rho(0) cell model was utilized to assess the function of mtDNA on radiosensitivity. Cell cycle distribution and reactive oxygen species (ROS) were analyzed to elucidate the potential mechanisms. For the whole group, the median follow-up time and overall survival time were 22.5 and 23.4 months, respectively. Patients with high mtDNA content had a marginally longer survival time than patients with low mtDNA content (P=0.053). Moreover, patients with high mtDNA content plus 10398G had a significantly longer overall survival time compared with those having low mtDNA content plus 10398A (47 vs. 27 months, P<0.05). In addition, multivariate analysis showed that stage and low mtDNA content plus 10398A were the two most independent prognostic factors. In vitro, the A549 rho(0) cells showed more resistance to radiation than rho(+) cells. Following radiation, rho(0) cells showed delayed G2 arrest and lower ROS level as compared to rho(+) cells. In conclusion, the present study suggests that in patients with NSCLC, low mtDNA content plus 10398A could be a marker of poor prognosis which is associated with resistance to anticancer treatment caused by low mtDNA content plus 10398A polymorphism resulting in mitochondrial dysfunction.

[583]

**TÍTULO / TITLE:** - Branched-chain amino acids to tyrosine ratio (BTR) predicts intrahepatic distant recurrence and survival for early hepatocellular carcinoma.

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

**REVISTA / JOURNAL:** - Hepatogastroenterology. 2013 Oct 2;60(128). doi: 10.5754/hge13488.

●● Enlace al texto completo (gratis o de pago) [5754/hge13488](#)

**AUTORES / AUTHORS:** - Ishikawa T; Kubota T; Horigome R; Kimura N; Honda H; Iwanaga A; Seki K; Honma T; Yoshida R N T

**RESUMEN / SUMMARY:** - :Background/Aims: The Child-Pugh classification system is the most widely used system for assessing hepatic functional reserve in HCC treatment. In the Child-Pugh classification system, serum albumin levels are used to accurately assess the status of protein metabolism and nutrition. To date, a lack of attention has been given to amino acid metabolism. In the present study, we investigated whether the branched-chain amino acids to tyrosine ratio (BTR) as an indicator of amino acid metabolism can serve as both a prognostic factor for early HCC and a predictive factor for recurrence. Methodology: We conducted a cohort study of 50 patients with stage I/II HCC enrolled between May 2002 and December 2010. It was investigated whether BTR can serve as both a prognostic factor and a predictive factor for HCC recurrence. Results: Overall survival rates were significantly higher in patients with high baseline BTR than in those with low BTR. Multivariate analysis showed that both BTR and serum albumin were prognostic factors, and that BTR was the best predictive factor for recurrence. Conclusions: BTR was a prognostic factor for early HCC and the most predictive factor for intrahepatic distant recurrence and contributing factors for survival.

[584]

**TÍTULO / TITLE:** - Aberrant expression of laminin gamma2 correlates with poor prognosis and promotes invasion in extrahepatic cholangiocarcinoma.

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

**REVISTA / JOURNAL:** - J Surg Res. 2013 Oct 2. pii: S0022-4804(13)00850-0. doi: 10.1016/j.jss.2013.09.008.

- Enlace al texto completo (gratis o de pago) [1016/j.jss.2013.09.008](#)

**AUTORES / AUTHORS:** - Liu W; Tian F; Jiang P; Zhao X; Guo F; Li X; Wang S

**INSTITUCIÓN / INSTITUTION:** - Institute of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University, Chongqing, China; Department of Infectious Disease, 324 Hospital of People's Liberation Army (PLA), Chongqing, China.

**RESUMEN / SUMMARY:** - BACKGROUND: To investigate the potential role of laminin gamma2 and its correlation with prognosis in patients with extrahepatic cholangiocarcinoma (CCA). MATERIALS AND METHODS: Laminin gamma2 expression was evaluated by immunohistochemistry in 72 extrahepatic CCA patients after surgical resection. Knockdown of laminin gamma2 was achieved via small interfering RNA transfection in the extrahepatic CCA cell line QBC939. RESULTS: Thirty-six of 72 extrahepatic CCAs (50%) stained positive for laminin gamma2 in two types of patterns: stromal staining (28/72, 39%) and cytoplasmic staining (24/72, 33%). All 16 paracancerous tissue samples showed negative staining. Both stromal and cytoplasmic laminin gamma2 expressions correlated with lymph node metastasis. Kaplan-Meier analysis showed that aberrant expression of laminin gamma2 correlated with poor overall survival and early recurrence. Cox regression analysis further demonstrated that laminin gamma2 expression was a significant independent predictor of poor overall survival and early recurrence. Immunofluorescence staining revealed cytoplasmic expression of laminin gamma2 in QBC939 cells. Knockdown of laminin gamma2 significantly reduced QBC939 cell invasion and migration. CONCLUSIONS:

Aberrant expression of laminin gamma2 correlates with poor prognosis and promotes invasion in extrahepatic CCA.

[585]

**TÍTULO / TITLE:** - ATM down-regulation is associated with poor prognosis in sporadic breast carcinomas.

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

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt421](#)

**AUTORES / AUTHORS:** - Bueno RC; Canevari RA; Villacis RA; Domingues MA; Caldeira JR; Rocha RM; Drigo SA; Rogatto SR

**INSTITUCIÓN / INSTITUTION:** - NeoGene Laboratory, Department of Urology, Sao Paulo State University, Botucatu.

**RESUMEN / SUMMARY:** - BACKGROUND: Ataxia telangiectasia-mutated (ATM) gene downexpression has been reported in sporadic breast carcinomas (BC); however, the prognostic value and mechanisms of ATM deregulation remain unclear. PATIENTS AND METHODS: ATM and miRNAs (miR-26a, miR-26b, miR-203, miR-421, miR-664, miR-576-5p and miR-18a) expression levels were evaluated by quantitative real-time PCR (RT-qPCR) in 52 BC and 3 normal breast samples. ATM protein expression was assessed by immunohistochemistry in 968 BC and 35 adjacent normal breast tissues. ATM copy number alteration was detected by array comparative genomic hybridization (aCGH) in 42 tumours. RESULTS: Low ATM levels were associated with tumour grade. Absence of ATM protein expression was associated with distant metastasis ( $P < 0.001$ ), reduced disease-free survival (DFS,  $P < 0.001$ ) and cancer-specific survival (CSS,  $P < 0.001$ ). Multivariate analysis indicated ATM protein expression as an independent prognostic marker for DFS ( $P = 0.001$ , HR = 0.579) and CSS ( $P = 0.001$ , HR = 0.554). ATM copy number loss was detected in 12% of tumours and associated with lower mRNA levels. miR-421 over-expression was detected in 36.5% of cases which exhibit lower ATM transcript levels ( $P = 0.075$ ,  $r = -0.249$ ). CONCLUSIONS: The data suggest that ATM protein expression is an independent prognostic marker in sporadic BC. Gene copy number loss and miR-421 over-expression may be involved in ATM deregulation in BC.

[586]

**TÍTULO / TITLE:** - Identification of candidate circulating cisplatin-resistant biomarkers from epithelial ovarian carcinoma cell secretomes.

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

**REVISTA / JOURNAL:** - Br J Cancer. 2013 Oct 31. doi: 10.1038/bjc.2013.687.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.687](#)

**AUTORES / AUTHORS:** - Teng PN; Wang G; Hood BL; Conrads KA; Hamilton CA; Maxwell GL; Darcy KM; Conrads TP

**INSTITUCIÓN / INSTITUTION:** - Women's Health Integrated Research Center at Inova Health System, Gynecologic Cancer Center of Excellence, 3289 Woodburn Road, Suite 370, Annandale, VA 22003, USA.

**RESUMEN / SUMMARY:** - Background: The majority of patients diagnosed with advanced epithelial ovarian carcinoma (EOC) relapse with resistant disease, and there

are no biomarkers that possess clinical utility to identify or monitor these patients. This study aimed to identify secreted proteins ('secretome') collected from human EOC cell lines that differ in their inherent platinum sensitivity. Methods: Secreted proteins collected from conditioned medium from ovarian cancer cell lines that vary in their sensitivity to cisplatin were digested with trypsin and analysed by liquid chromatography-tandem mass spectrometry for peptide identification. Results: Of the 1688 proteins identified, 16 possessed significant differential abundances ( $P < 0.05$ ) between the platinum-resistant and -sensitive cell lines. A number of these were verified by immunoblot, including COL11A1, which was also found to be associated with worse progression-free survival (PFS;  $N=723$ ) and overall survival (OS;  $N=1183$ ) as assessed from publicly available transcript expression data from ovarian cancer tumour specimens. Conclusion: Secretome proteomics of EOC cells resulted in the identification of a novel candidate biomarker, COL11A1. The expression level of COL11A1 correlates to worse PFS and OS, and is predicted to reside in peripheral circulation making this an attractive candidate for validation in sera as a biomarker of cisplatin resistance and poor outcome. British Journal of Cancer advance online publication, 31 October 2013; doi:10.1038/bjc.2013.687 [www.bjccancer.com](http://www.bjccancer.com).

[587]

**TÍTULO / TITLE:** - Antitumor activity of neurokinin-1 receptor antagonists in MG-63 human osteosarcoma xenografts.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):137-46. doi: 10.3892/ijo.2013.2164. Epub 2013 Nov 5.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.2164](#)

**AUTORES / AUTHORS:** - Munoz M; Berger M; Rosso M; Gonzalez-Ortega A; Carranza A; Covenas R

**INSTITUCIÓN / INSTITUTION:** - Virgen del Rocio University Hospital, Research Laboratory on Neuropeptides, Seville, España.

**RESUMEN / SUMMARY:** - Osteosarcoma is a highly malignant bone tumor in children and adolescents. Aprepitant is a selective high affinity antagonist of the human neurokinin1 (NK1) receptor (NK1R) with robust antitumor activity. No data exist on the presence of NK1R in osteosarcoma and whether this tumor responds to NK1R antagonists. Here, we analyzed the expression of NK1R in the human osteosarcoma cell line MG-63 with western blot analysis and PCR and found significant expression both at the protein and mRNA levels. We further studied the growth inhibitory capacity of aprepitant and other NK1R antagonists on MG-63 in vitro using an MTS cytotoxicity assay and DAPI staining. All antagonists induced tumor growth inhibition and apoptosis. Synergism was observed for the combination of L-733,060 with common cytostatic drugs in MG-63, but not in non-malignant HEK293 cells. Pretreatment of HEK293 with L-733,060 prior to exposure to cytostatic drugs partially protected HEK293 cells from inhibition by these drugs. Furthermore, nanomolar concentrations of substance P (SP), the natural ligand of the NK1R, increased the growth rate of MG63 cells and micromolar concentrations of aprepitant inhibited SP-induced growth in a dose dependent manner. In vivo, a xenograft for MG-63 was created in nude mice and treated with peritumoral s.c. injections of fosaprepitant, which resulted in a significant reduction of tumor volume. Collectively, we demonstrated for the first time that the

NK1R is expressed in human osteosarcoma cell line MG63 and that this receptor can be targeted with NK1R antagonists both in vitro as well as in vivo.

[588]

**TÍTULO / TITLE:** - Thyroid transcription factor-1 (ttf-1) immunoreactivity is an adverse prognostic factor in endometrioid adenocarcinoma of the uterine corpus.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Nov 23. doi: 10.1111/his.12332.

●● Enlace al texto completo (gratis o de pago) [1111/his.12332](#)

**AUTORES / AUTHORS:** - Ervine A; Leung S; Gilks CB; McCluggage WG

**INSTITUCIÓN / INSTITUTION:** - Dept of Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom.

**RESUMEN / SUMMARY:** - AIMS: It is known that thyroid transcription factor-1 (TTF-1) is expressed in a small percentage of primary gynaecological adenocarcinomas.

Following the observation of TTF-1 positivity in a number of endometrioid adenocarcinomas of the uterine corpus which behaved aggressively, we stained a large series of endometrial adenocarcinomas of various types to investigate whether its expression is of prognostic significance. METHODS AND RESULTS: TTF-1 immunohistochemistry was performed on tissue microarrays containing 102 low grade (grade 1 or 2) endometrioid adenocarcinomas, 101 grade 3 endometrioid adenocarcinomas, 89 serous adenocarcinomas and 29 clear cell carcinomas. All categories of endometrial adenocarcinoma exhibited TTF-1 staining in a small subset of cases (2% low grade endometrioid, 11% grade 3 endometrioid, 9% serous, 7% clear cell). TTF-1 was less expressed in low grade endometrioid adenocarcinomas compared to other subtypes. Endometrioid adenocarcinomas which expressed TTF-1 had a statistically significant worse prognosis with poorer disease specific survival and this was also statistically significant in the group of low grade endometrioid adenocarcinomas. CONCLUSIONS: Our study confirms that TTF-1 is positive in a small, but not insignificant, proportion of endometrial adenocarcinomas. TTF-1 positivity in low grade endometrioid adenocarcinomas is a poor prognostic factor. This article is protected by copyright. All rights reserved.

[589]

**TÍTULO / TITLE:** - Signaling Pathways Modulating Dependence of Lung Cancer on Mutant Epidermal Growth Factor Receptor and Mechanisms of Intrinsic and Acquired Resistance to Tyrosine Kinase Inhibitors.

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

**REVISTA / JOURNAL:** - Curr Pharm Des. 2013 Nov 5.

**AUTORES / AUTHORS:** - Wannesson L; Viteri S; Costa C; Karachaliou N; Molina-Vila MA; Rosell R

**INSTITUCIÓN / INSTITUTION:** - Oncology Institute of Southern Switzerland, CH6500 Bellinzona, Switzerland. [Luciano.Wannesson@eoc.ch](mailto:Luciano.Wannesson@eoc.ch).

**RESUMEN / SUMMARY:** - A new era in lung cancer targeted therapy arrived with the discovery of a subset of lung adenocarcinomas harboring activating mutations of the epidermal growth factor receptor (EGFR), whose tyrosine kinase activity can be selectively blocked by small molecule pharmaceuticals referred as tyrosine kinase

inhibitors (TKIs). This was the starting point for a less toxic and more effective treatment strategy for a disease that has historically presented as chemorefractory and highly lethal. In spite of this progress, only 80% of the patients treated with this class of compounds will obtain a clinical benefit, of variable magnitude and duration, with remaining patients being primarily refractory to the treatment. Moreover, responding tumors will eventually develop acquired resistance to TKIs and progress to more advanced stages. In this review we summarize the current knowledge with regard to the mechanisms leading to tumor regression and the modifiers of this primary response that determine significant variability in sensitivity of tumors harboring EGFR activating mutations, ranging from complete remission to primary refractoriness. We also analyze the mechanisms of secondary resistance and the strategies the scientific community is exploring in order to overcome these barriers.

[590]

**TÍTULO / TITLE:** - Tyrosine kinase inhibitor-induced vasculopathy in clear cell renal cell carcinoma: an unrecognized antitumour mechanism.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Sep 7. doi: 10.1111/his.12277.

●● [Enlace al texto completo \(gratis o de pago\) 1111/his.12277](#)

**AUTORES / AUTHORS:** - Tsuzuki T; Sassa N; Shimoyama Y; Morikawa T; Shiroki R; Kuroda M; Fukatsu A; Kuwahara K; Yoshino Y; Hattori R; Gotoh M

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Nagoya Daini Red Cross Hospital, Nagoya, Japan.

**RESUMEN / SUMMARY:** - **AIMS:** To evaluate the pathological features of clear cell renal cell carcinoma (CCRCC) treated with tyrosine kinase inhibitors (TKIs), and to elucidate the mechanism of action of TKIs. **METHODS AND RESULTS:** Twenty cases of CCRCC treated with TKIs (sorafenib or sunitinib) were retrospectively analysed: 16 were patients who had undergone radical nephrectomy after neoadjuvant TKI therapy, and four were autopsy cases of patients who received TKI treatment. All tumours had two distinct regions: one characterized by necrosis and/or degeneration, indicating antitumour activity; and the other characterized by no or few pathological changes, indicating the absence of antitumour activity. Vasculopathy of tumour vessels was observed in or adjacent to the necrotic or degenerative areas; a decreased density of endothelial cells was noted in the tumour vessels. Few or no changes of vasculopathy were observed in tumour vessels in the other CCRCC areas, indicating the absence or low levels of antitumour activity. **CONCLUSIONS:** This is the first pathological report of vasculopathy in TKI-treated CCRCC cases. Our data suggest that TKIs initially induce vasculopathy in tumour vessels, and consequently cause reduction or diminution of blood supply to the CCRCCs, resulting in antitumour activity characterized by necrosis and hyalinization.

[591]

**TÍTULO / TITLE:** - Protein Z/protein Z-dependent protease inhibitor system in loco in human gastric cancer.

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

**REVISTA / JOURNAL:** - Ann Hematol. 2013 Oct 26.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1941-8](https://doi.org/10.1007/s00277-013-1941-8)

**AUTORES / AUTHORS:** - Sierko E; Wojtukiewicz MZ; Zimnoch L; Tokajuk P; Ostrowska-Cichońska K; Kisiel W

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Medical University, 12 Ogrodowa St., Białystok, Poland, [ewa.sierko@iq.pl](mailto:ewa.sierko@iq.pl).

**RESUMEN / SUMMARY:** - In gastric cancer, hemostatic system components contribute to cancer progression, as activation of factor X (FX) was observed. The protein Z (PZ)/protein Z-dependent protease inhibitor (ZPI) complex inhibits factor Xa proteolytic activity. The purpose of this study was to determine the distribution of ZPI and PZ in relation to FX, and prothrombin fragment (F1 + 2), a standard marker for blood coagulation activation, in human gastric cancer tissue. ABC procedures and a double staining method employed polyclonal antibodies against PZ, FX, and F1 + 2 and a monoclonal antibody against ZPI. In situ hybridization (ISH) methods employed biotin-labeled 25-nucleotide single-stranded DNA probes directed to either PZ or ZPI mRNAs. FX and components of PZ/ZPI coagulation inhibitory system were observed in cancer cells. F1 + 2 was observed in gastric cancer cells as well. Double staining studies revealed FX/PZ, FX/ZPI, and PZ/ZPI co-localization on gastric cancer cells. ISH studies demonstrated the presence of PZ mRNA and ZPI mRNA in gastric cancer cells indicating induced synthesis of these proteins. The co-localization of PZ/ZPI and FX in gastric cancer cells indicates in loco that these proteins may play a role in anticoagulant events at the tumor tissue.

[592]

**TÍTULO / TITLE:** - PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies.

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

**REVISTA / JOURNAL:** - Ann Oncol. 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt384](https://doi.org/10.1093/annonc/mdt384)

**AUTORES / AUTHORS:** - Lee JM; Ledermann JA; Kohn EC

**INSTITUCIÓN / INSTITUTION:** - Molecular Signaling Section, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, USA.

**RESUMEN / SUMMARY:** - Poly(ADP-ribose)polymerase inhibitors (PARPi) have shown promising activity in patients with BRCA1/2 mutation-associated (BRCA1/2MUT+) ovarian and breast cancers. Accumulating evidence suggests that PARPi may have a wider application in the treatment of sporadic high-grade serous ovarian cancer, and cancers defective in DNA repair pathways, such as prostate, endometrial, and pancreatic cancers. Several PARPi are currently in phase ½ clinical investigation, with registration trials now being designed. Olaparib, one of the most studied PARPi, has demonstrated activity in BRCA1/2MUT+ and BRCA-like sporadic ovarian and breast cancers, and looks promising in prostate and pancreatic cancers. Understanding more about the molecular abnormalities involved in BRCA-like tumors, exploring novel therapeutic trial strategies and drug combinations, and defining potential predictive biomarkers, is critical to rapidly advancing the field of PARPi therapy and improve clinical outcomes.

[593]

**TÍTULO / TITLE:** - Clinical Application of Pharmacogenetics of non-small cell lung cancer (NSCLC): time to “work it out”?

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

**REVISTA / JOURNAL:** - Curr Pharm Des. 2013 Nov 5.

**AUTORES / AUTHORS:** - Galvani E; Toffalorio F; Peters GJ; De Pas T; Giovannetti E

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology VU University Medical Center De Boelelaan 1117 1081 HV Amsterdam The Netherlands.

[elisa.giovannetti@gmail.com](mailto:elisa.giovannetti@gmail.com).

**RESUMEN / SUMMARY:** - The disappointing results in long-term survival of patients affected by non-small cell lung cancer (NSCLC) may be attributed, at least in part, to the lack of knowledge on the way by which genetic characteristics in normal and neoplastic cells affect responsiveness as well as metabolism of chemotherapy and new targeted agents. This issue deserves further pharmacogenetics studies, in order to select patients who may benefit from treatments that best match the individual and tumor genetic profile, thus allowing maximum activity and minimal toxicity. Even if most meta-analyses in NSCLC yielded contradictory results, a number of potential biomarkers for sensitivity/resistance to conventional chemotherapeutic agents such as gemcitabine, platinum-compounds, pemetrexed and taxanes have been proposed. Similarly, recent studies suggested the role of key polymorphisms in the prediction of toxicity to EGFR-targeted agents. However, larger prospective randomized trials of customized therapy to validate these biomarkers are still needed. Other critical points include the standardization of technical procedures and additional investigation to unravel pivotal factors influencing genotype-phenotype relationships. From this perspective, functional studies to clarify pharmacokinetics/pharmacodynamics interactions are critical for the pharmacogenetic optimization of anti-cancer regimens. Finally, due to the development of high-throughput technologies to decipher genetic characteristics, the traditional pharmacogenetic approach relying only on candidate genes suspected of affecting drug response/metabolism can be implemented by whole exome analyses providing further lists of potential predictive alleles. The clinical implementation of such pharmacogenetics/genomics studies as well as of therapeutic drug monitoring could enable clinicians to personalize treatment to enhance efficacy and/or limit toxicity.

[594]

**TÍTULO / TITLE:** - Hepatocyte growth factor and HER2/neu downregulate expression of apoptosis-inducing factor in non-small cell lung cancer.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Nov 25. doi: 10.3892/or.2013.2867.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2867](#)

**AUTORES / AUTHORS:** - Chiang YY; Chow KC; Lin TY; Chiang IP; Fang HY

**INSTITUCIÓN / INSTITUTION:** - Department of Dental Laboratory Technology, Central Taiwan University of Science and Technology, Taichung, Taiwan, R.O.C.

**RESUMEN / SUMMARY:** - Our previous study showed that patients with advanced stages of non-small cell lung cancer (NSCLC) were frequently detected with upregulation of hepatocyte growth factor (HGF). In vitro, HGF reduced expression of apoptosis-inducing factor (AIF) and cisplatin sensitivity in NSCLC cells. The effect of HGF was via HGF receptor (c-MET) and the downstream effector, focal adhesion

kinase (FAK). In this study, we determined the prognostic value of AIF in NSCLC patients. AIF expression was determined by immunohistochemistry and immunoblotting. Our data show that AIF expression was associated with better prognosis. Expression of AIF inversely correlated with that of positive NSCLC markers, e.g., dihydrodiol dehydrogenase (DDH), c-MET, short oncostatin M receptor (OSMRs), matrix metalloproteinase (MMP)-1, and HER2/neu, which were closely associated with drug resistance, tumor recurrence, metastasis and poor prognosis. Noteworthy, silencing of HER2/neu gene expression increases AIF level and drug sensitivity. Addition of HGF inhibits AIF expression in HER2/neu-silenced cells. These results suggested that both HGF and HER2/neu affect drug resistance by regulating AIF expression in NSCLC.

[595]

**TÍTULO / TITLE:** - High expression of APAF-1 elevates erythroid apoptosis in iron overload myelodysplastic syndrome.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 19.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1294-x](#)

**AUTORES / AUTHORS:** - Gu S; Zhao Y; Guo J; Xu F; Fei C; Zhang X; Xiao C; Chang C; Li X

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University, No.600, Yi Shan Road, Shanghai, 200233, China.

**RESUMEN / SUMMARY:** - Apoptotic protease-activating factor 1 (APAF-1) is a central component of the intrinsic pathway of apoptosis. Our study aims at searching the role of APAF-1 in iron overload myelodysplastic syndrome (MDS). Erythroid apoptosis rate, mRNA expression levels of APAF-1, and caspase-9 activity were determined by flow cytometry, quantitative real-time PCR, and colorimetric assay in MDS patients, respectively. In addition, K562 and MDS-L cell lines were incubated with different concentrations of ferric ammonium citrate (FAC) or ferric ammonium citrate + desferrioxamine (FAC + DFO) in vitro to observe the alteration in erythrocyte apoptosis rate, APAF-1 mRNA, and protein expression levels. Moreover, as control, erythroid apoptosis rate and APAF-1 mRNA expression were detected after silencing APAF-1 expression by endoribonuclease-prepared small interfering RNAs (esiRNAs) in K562 and MDS-L cell lines. Both erythroid apoptosis rate and APAF-1 mRNA expression of the iron overload (IO) group were significantly higher than those of the non-IO group ( $P < 0.001$  and  $P < 0.001$ ). There is a significant difference of caspase-9 activity between the IO group and the non-IO group ( $P < 0.001$ ). Erythroid apoptosis rate and APAF-1 mRNA expression of K562 and MDS-L cell lines significantly elevated after FAC incubation in different concentrations ( $P < 0.001$  and  $P < 0.001$  for K562;  $P < 0.001$  and  $P < 0.001$  for MDS-L), while erythroid apoptosis rate and APAF-1 mRNA expression in the FAC + DFO group declined ( $P < 0.001$  and  $P < 0.001$  for K562;  $P < 0.001$  and  $P < 0.001$  for MDS-L). After silencing of APAF-1 expression with specific esiRNAs, erythroid apoptosis rate and APAF-1 mRNA expression of K562 and MDS-L cell lines markedly decreased ( $P < 0.001$  and  $P < 0.001$  for K562;  $P < 0.001$  and  $P < 0.001$  for MDS-L). APAF-1 plays an important role in iron-induced erythroid apoptosis increase in MDS.

[596]

**TÍTULO / TITLE:** - Sterol regulatory element-binding protein-1/fatty Acid synthase involvement in proliferation inhibition and apoptosis promotion induced by progesterone in endometrial cancer.

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

**REVISTA / JOURNAL:** - Int J Gynecol Cancer. 2013 Nov;23(9):1629-34. doi: 10.1097/IGC.0000000000000004.

●● Enlace al texto completo (gratis o de pago) [1097/IGC.0000000000000004](#)

**AUTORES / AUTHORS:** - Qiu C; Dongol S; Lv QT; Gao X; Jiang J

**INSTITUCIÓN / INSTITUTION:** - \*Department of Obstetrics and Gynecology, Qi Lu Hospital, Shangong University, Jinan, Shandong, China; daggerDepartment of Pharmaceutical Chemistry, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China; and double daggerPhysical Examination Centre, Qi Lu Hospital, Shangong University, Jinan, Shandong, China.

**RESUMEN / SUMMARY:** - BACKGROUND: The number of endometrial cancer (EC) cases is escalating rapidly, with no evident improvements in survival rates. The downregulation of progesterone receptor, resulting in progestin resistance, is presently a major problem regarding the therapeutic aspect. On the basis of this, we can focus more on the downstream signaling pathways that are controlled by progesterone. Lipid biosynthesis mediated by sterol regulatory element-binding protein-1/fatty acid synthase (SREBP-1/FASN) is of utmost importance to the growth and the proliferation of EC cells, so we hypothesize that SREBP-1/FASN might be involved in suppressing the proliferation and promoting apoptosis in EC cells through the effects induced by progesterone. MATERIAL AND METHODS: The Cell Counting Kit-8 was used to analyze the growth inhibition ratio of Ishikawa cells upon treatment with megestrol acetate (MA; MA is a progesterone derivative, also known as 17alpha-acetoxy-6-dehydro-6-methylprogesterone) and to determine the 50% inhibitory concentration. Apoptosis ratio was analyzed by treatment of the cells with MA at 50% inhibitory concentration at different time intervals using Annexin V-FITC/propidium iodide. The protein and messenger RNA levels of SREBP-1 and FASN were compared between the experimental and control groups (MA-treated Ishikawa cells were considered to be the experimental group). RESULTS: The experimental group showed obvious growth inhibition that was time and concentration dependent. The apoptosis ratio was also significantly higher in the experimental group compared with the control group ( $P < 0.01$ ). The protein and messenger RNA levels of SREBP-1 and FASN were significantly reduced by MA too. CONCLUSIONS: Sterol regulatory element-binding protein-1/FASN is involved in the proliferation suppression and apoptosis promotion brought about by MA in Ishikawa cells.

[597]

**TÍTULO / TITLE:** - Reduced expression of alphaGlcNAc in Barrett's oesophagus adjacent to Barrett's adenocarcinoma - a possible biomarker to predict the malignant potential of Barrett's oesophagus.

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

**REVISTA / JOURNAL:** - Histopathology. 2013 Oct 1. doi: 10.1111/his.12296.

- Enlace al texto completo (gratis o de pago) [1111/his.12296](#)

**AUTORES / AUTHORS:** - Iwaya Y; Hasebe O; Koide N; Kitahara K; Suga T; Shinji A; Muraki T; Yokosawa S; Yamada S; Arakura N; Tanaka E; Nakayama J

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Pathology, Shinshu University Graduate School of Medicine, Matsumoto, Japan; Department of Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan.

**RESUMEN / SUMMARY:** - AIMS: Gastric gland mucin contains O-glycans exhibiting terminal alpha1,4-linked N-acetylglucosamine residues (alphaGlcNAc). Recently we demonstrated that mice deficient in alphaGlcNAc in gastric gland mucin develop gastric adenocarcinoma spontaneously, indicating that alphaGlcNAc is a tumour suppressor for gastric cancer. However, the role of alphaGlcNAc in Barrett's oesophagus (BO) remains unknown. In this study, we investigated whether reduced alphaGlcNAc expression in BO is associated with development of Barrett's adenocarcinoma (BAC). METHODS AND RESULTS: Thirty-five BO lesions adjacent to BAC were examined by immunohistochemistry for alphaGlcNAc, MUC6 and CDX2. As controls, 35 BO lesions without BAC obtained from patients with oesophageal squamous cell carcinoma were also analysed. Expression of alphaGlcNAc relative to its scaffold MUC6 in BO adjacent to BAC was reduced significantly compared to control BO. Decreased alphaGlcNAc expression in BO adjacent to BAC was particularly significant in patients with smaller tumour size (<20 mm) and minimal invasion of tumour cells to the superficial muscularis mucosae. There was also a significant inverse correlation between alphaGlcNAc and CDX2 expression in BO adjacent to BAC. CONCLUSIONS: Decreased expression of alphaGlcNAc compared with MUC6 in BO is a possible hallmark in predicting BAC development.

[598]

**TÍTULO / TITLE:** - Long-term remission achieved via combined chemotherapy and radiotherapy in a non-resectable granulocyte colony-stimulating factor producing pleomorphic carcinoma of the lung.

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

**REVISTA / JOURNAL:** - Intern Med. 2013;52(19):2259-63. Epub 2012 Mar 1.

**AUTORES / AUTHORS:** - Yamamoto M; Manabe S; Moriyama Y; Ishii H; Tanaka S; Takahashi R; Tomaru K; Kobayashi N; Kudo M; Sasaki M; Inayama Y; Kaneko T; Ishigatsubo Y

**INSTITUCIÓN / INSTITUTION:** - Respiratory Medicine, Yokohama City University Hospital, Japan.

**RESUMEN / SUMMARY:** - The prognosis is poor for patients with advanced pleomorphic carcinoma of the lung due to the generally limited response to chemotherapy and/or radiotherapy. It has been suggested the production of granulocyte colony-stimulating factor (G-CSF) by cancer cells may aggravate the disease progression. We herein report a case of a 73-year-old Japanese man with advanced G-CSF-producing pleomorphic carcinoma of the lung. First-line chemotherapy with carboplatin and paclitaxel had been suspended. Subsequent radiotherapy achieved a moderate volume reduction and an amelioration of the excessive G-CSF-related complications. Six cycles of second-line chemotherapy with docetaxel administered with good results. These combined treatments resulted in long term survival without progression of the disease.

[599]

**TÍTULO / TITLE:** - IntApop: A web service for predicting apoptotic protein interactions in humans.

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

**REVISTA / JOURNAL:** - Biosystems. 2013 Dec;114(3):238-44. doi: 10.1016/j.biosystems.2013.09.007. Epub 2013 Oct 8.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1016/j.biosystems.2013.09.007](#)

**AUTORES / AUTHORS:** - Zhou N; Zhang J; Feng L; Lu B; Wang Z; Sun R; Wu C; Bao J  
**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences & Key Laboratory of Bio-resources, Ministry of Education, Sichuan University, Chengdu 610064, China.

**RESUMEN / SUMMARY:** - Apoptosis, a type of cell death, is necessary for maintaining tissue homeostasis and removing malignant cells. Interrupted apoptosis process contributes to carcinogenesis, developmental defects, autoimmune diseases and neurological disorders. Due to the complexity of the process, the molecular dynamics and relative interactions of individual proteins responsible for the activation or inhibition of apoptosis should be researched systematically. In this study, we integrate known protein interactions from databases DIP, IntAct, MINT, HPRD and BioGRID by Naive Bayes classifier. The receiver operation characteristic (ROC) curve with the area under the ROC curve (AUC) of 0.797 indicates it has a good performance in prediction. Then, we predict the global human apoptotic protein interactions network. Within it, we not only identify the already known interactions of caspases (caspase-8/-10, caspase-9, caspase-3/-6/-7) and Bcl-2 family, but also reveal that Bid can interact with casein kinases (CSK21/22/2B, KC1A, KC1E); both of B2LA1 and B2CL2 can interact with Bid, Bax and Bak; caspase-8 interacts with autophagic proteins (MLP3B, MLP3A and LRRk2). Consequently, we make an initial step to develop the web service IntApop that provides an appropriate platform for apoptosis researchers, systems biologists and translational clinician scientists to predict apoptotic protein interactions in human. In addition, the interaction network can be visualized online, making it a widely applicable systems biology tool for apoptosis and cancer researchers.

[600]

**TÍTULO / TITLE:** - CR108, a novel vitamin K3 derivative induces apoptosis and breast tumor inhibition by reactive oxygen species and mitochondrial dysfunction.

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

**REVISTA / JOURNAL:** - Toxicol Appl Pharmacol. 2013 Oct 12. pii: S0041-008X(13)00438-9. doi: 10.1016/j.taap.2013.10.007.

●● [Enlace al texto completo \(gratis o de pago\)](#) [1016/j.taap.2013.10.007](#)

**AUTORES / AUTHORS:** - Yang CR; Liao WS; Wu YH; Murugan K; Chen C; Chao JI  
**INSTITUCIÓN / INSTITUTION:** - Department of Biological Science and Technology, National Chiao Tung University, Hsinchu 30068, Taiwan.

**RESUMEN / SUMMARY:** - Vitamin K3 derivatives have been shown to exert anticancer activities. Here we show a novel vitamin K3 derivative (S)-2-(2-hydroxy-3-methylbutylthio)naphthalene-1,4-dione, which is named as CR108 that induces apoptosis and tumor inhibition through reactive oxygen species (ROS) and

mitochondrial dysfunction in human breast cancer. CR108 is more effective on the breast cancer cell death than other vitamin K3 derivatives. Moreover, CR108 induced apoptosis in both the non-HER-2-overexpressed MCF-7 and HER-2-overexpressed BT-474 breast cancer cells. CR108 caused the loss of mitochondrial membrane potential, cytochrome c released from mitochondria to cytosol, and cleaved PARP proteins for apoptosis induction. CR108 markedly increased ROS levels in breast cancer cells. N-acetylcysteine (NAC), a general ROS scavenger, completely blocked the CR108-induced ROS levels, mitochondrial dysfunction and apoptosis. Interestingly, CR108 increased the phosphorylation of p38 MAP kinase but conversely inhibited the survivin protein expression. NAC treatment prevented the activation of p38 MAP kinase and rescued the survivin protein levels. SB202190, a specific p38 MAP kinase inhibitor, recovered the survivin protein levels and attenuated the cytotoxicity of CR108-treated cells. Furthermore, CR108 inhibited the xenografted human breast tumor growth in nude mice. Together, we demonstrate that CR108 is a novel vitamin K3 derivative that induces apoptosis and tumor inhibition by ROS production and mitochondrial dysfunction and associates with the phosphorylation of p38 MAP kinase and the inhibition of survivin in the human breast cancer.

[601]

**TÍTULO / TITLE:** - Compound K, a metabolite of ginseng saponin, inhibits colorectal cancer cell growth and induces apoptosis through inhibition of histone deacetylase activity.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):1907-14. doi: 10.3892/ijo.2013.2129. Epub 2013 Oct 4.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2129](#)

**AUTORES / AUTHORS:** - Kang KA; Piao MJ; Kim KC; Zheng J; Yao CW; Cha JW; Kim HS; Kim DH; Bae SC; 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:** - In this study, we investigated the molecular mechanisms underlying the anti-proliferative effects of Compound K, with specific reference to histone modification. Exposure of HT-29 human colon cancer cells to Compound K resulted in time-dependent inhibition of histone deacetylase (HDAC) activity, mRNA and protein expression. Compound K treatment induced unmethylation of the RUNX3 promoter region such as TSA treatment and an accumulation of acetylated histones H3 and H4 within the total cellular chromatin, resulting in an enhanced ability of these histones to bind to the promoter sequences of the tumor suppressor gene Runt-related transcription factor 3 (RUNX3). Treatment of cells with Compound K increased the mRNA and protein expression of RUNX3, as well as p21, a downstream target of RUNX3. These alterations were consistent with cell cycle arrest at the G0/G1 phases and induction of apoptosis. Our results provide new insights into the mechanisms of Compound K action in human colorectal cancer cells and suggest that HDAC inhibition presents a novel approach to prevent or treat colorectal cancer.

[602]

**TÍTULO / TITLE:** - Folic acid-modified dendrimer-DOX conjugates for targeting cancer chemotherapy.

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

**REVISTA / JOURNAL:** - J Control Release. 2013 Nov 28;172(1):e55-6. doi: 10.1016/j.jconrel.2013.08.115.

●● Enlace al texto completo (gratis o de pago) [1016/j.jconrel.2013.08.115](#)

**AUTORES / AUTHORS:** - Zhang M; Shi X

**INSTITUCIÓN / INSTITUTION:** - College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China.

[603]

**TÍTULO / TITLE:** - Gender difference in tumor necrosis factor-alpha production in human neutrophils stimulated by lipopolysaccharide and interferon-gamma.

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

**REVISTA / JOURNAL:** - Biochem Biophys Res Commun. 2013 Nov 8;441(1):220-5. doi: 10.1016/j.bbrc.2013.10.042. Epub 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.10.042](#)

**AUTORES / AUTHORS:** - Aomatsu M; Kato T; Kasahara E; Kitagawa S

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Osaka City University, Graduate School of Medicine, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.

**RESUMEN / SUMMARY:** - The gender difference in tumor necrosis factor-alpha (TNF-alpha) production in human neutrophils stimulated by lipopolysaccharide (LPS) and interferon-gamma (IFN-gamma) was explored by using peripheral blood neutrophils from young men and women. As compared with female neutrophils, male neutrophils released greater amounts of TNF-alpha, and exhibited stronger activation of mitogen-activated protein kinases and phosphatidylinositol 3-kinase in response to LPS stimulation. LPS-induced TNF-alpha production was markedly enhanced by pretreatment of cells with IFN-gamma, and IFN-gamma-mediated priming in male neutrophils was significantly greater than that in female neutrophils. Male neutrophils showed higher expression of TLR4, but not IFN-gamma receptors, than female neutrophils, and its expression was increased by stimulation with IFN-gamma or IFN-gamma plus LPS. These findings indicate that male neutrophils show higher responsiveness to stimulation with LPS and IFN-gamma than female neutrophils, and suggest that the gender difference in neutrophil responsiveness to LPS and IFN-gamma is partly responsible for that in the outcome of sepsis, in which premenopausal women show a favorable prognosis as compared with men.

[604]

**TÍTULO / TITLE:** - Radiotherapy and concurrent metronomic chemotherapy in hormone-refractory prostate carcinoma: a Phase I study.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4585-9.

**AUTORES / AUTHORS:** - Morganti AG; Massaccesi M; Caravatta L; Macchia G; Picardi V; Deodato F; Ippolito E; Mignogna S; Ferro M; Cilla S; Mattiucci GC; Valentini V

**INSTITUCIÓN / INSTITUTION:** - Department of Radiotherapy, Research and Care Foundation “Giovanni Paolo II”, Catholic University of Sacred Heart, Largo A. Gemelli 1, 86100 Campobasso, Italy. [gmacchia@rm.unicatt.it](mailto:gmacchia@rm.unicatt.it).

**RESUMEN / SUMMARY:** - AIM: To determine the maximum tolerated dose of hypofractionated radiotherapy (HFRT) plus concurrent metronomic chemotherapy in patients with hormone-refractory prostate cancer (HRPC). PATIENTS AND METHODS: A Phase I clinical trial was performed with cohorts of three to six patients per group. Eligible patients had HRPC without distant metastases. The radiotherapy dose was escalated in a stepwise fashion as follows: 60, 65, and 70 Gy at levels 1, 2, and 3, respectively (25 fractions: levels 1-2, and 26 fractions: level 3). RESULTS: Nine patients were enrolled. The radiotherapy dose was escalated from 60 to 70 Gy without any dose-limiting toxicity. The most common grade ½ toxicities were hematuria, dysuria, diarrhea and rectal-perirectal pain. The overall objective response rate was 9/9 (100%) (95% CI=66.4%-100%). The median time-to-progression was 19 months. CONCLUSION: In the challenging setting of HRPC, HFRT up to 70 Gy with concurrent metronomic chemotherapy was well-tolerated and yielded encouraging disease control.

[605]

**TÍTULO / TITLE:** - Spacer length impacts the efficacy of targeted docetaxel conjugates in prostate-specific membrane antigen expressing prostate cancer.

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

**REVISTA / JOURNAL:** - J Drug Target. 2013 Dec;21(10):968-80. doi: 10.3109/1061186X.2013.833207.

●● Enlace al texto completo (gratis o de pago) [3109/1061186X.2013.833207](#)

**AUTORES / AUTHORS:** - Peng ZH; Sima M; Salama ME; Kopeckova P; Kopecek J

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutics and Pharmaceutical Chemistry/CCCD .

**RESUMEN / SUMMARY:** - Abstract Combination of targeted delivery and controlled release is a powerful technique for cancer treatment. In this paper, we describe the design, synthesis, structure validation and biological properties of targeted and non-targeted N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-docetaxel conjugates. Docetaxel (DTX) was conjugated to HPMA copolymer via a tetrapeptide spacer (-GFLG-). 3-(1,3-dicarboxypropyl)-ureido]pentanedioic acid (DUPA) was used as the targeting moiety to actively deliver DTX for treatment of Prostate-Specific Membrane Antigen (PSMA) expressing prostate cancer. Short and long spacer DUPA monomers were prepared, and four HPMA copolymer - DTX conjugates (non-targeted, two targeted with short spacer of different molecular weight and targeted with long spacer) were prepared via Reversible Addition-Fragmentation Chain Transfer (RAFT) copolymerization. Following confirmation of PSMA expression on C4-2 cell line, the DTX conjugates' in vitro cytotoxicity was tested against C4-2 tumor cells and their anticancer efficacies were assessed in nude mice bearing s.c. human prostate adenocarcinoma C4-2 xenografts. The in vivo results show that the spacer length between targeting moieties and HPMA copolymer backbone can significantly affect the treatment efficacy of DTX conjugates against C4-2 tumor bearing nu/nu mice. Moreover, histological analysis indicated that the DUPA-targeted DTX conjugate with longer spacer had no toxicity in major organs of treated mice.

[606]

**TÍTULO / TITLE:** - Irreversible EGFR Inhibitors in the Treatment of Advanced NSCLC.

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

**REVISTA / JOURNAL:** - Curr Pharm Des. 2013 Nov 5.

**AUTORES / AUTHORS:** - Maione P; Rossi A; Bareschino M; Sacco PC; Schettino C; Casaluce F; Sgambato A; Gridelli C

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology "S.G. Moscati" Hospital Contrada Amoretta - 83100 Avellino (Italy). [pmaione@libero.it](mailto:pmaione@libero.it).

**RESUMEN / SUMMARY:** - The epidermal growth factor receptor (EGFR) is among the most important target in the treatment of advanced non-small cell lung cancer (NSCLC). Erlotinib and gefitinib, two small molecules, are reversible EGFR tyrosine kinase inhibitors (TKIs). Non-small cell lung cancers with EGFR mutations, are characterized by excellent responses when treated with the EGFR-TKIs gefitinib and erlotinib. However, all the patients with tumors harbouring EGFR mutations experience disease progression after a median of 10 to 14 months of treatment with gefitinib or erlotinib. A group of new generation EGFR-TKIs irreversibly inhibit EGFR-TK and represent one of the strategies that may potentially overcome the acquired resistance to gefitinib and erlotinib or achieve better outcomes than reversible inhibitors in the first-line treatment of EGFR mutant lung cancers. Afatinib (BIBW 2992) and PF299804 are the irreversible EGFR-TKIs with the most relevant data in the treatment of advanced NSCLC, as primary EGFR-targeted therapy and after resistance to reversible EGFR-TKIs. However, to date, the role of irreversible EGFR inhibitors remains to be defined.

[607]

**TÍTULO / TITLE:** - The immunogenicity of a novel cytotoxic T lymphocyte epitope from tumor antigen PL2L60 could be enhanced by 4-chlorophenylalanine substitution at position 1.

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

**REVISTA / JOURNAL:** - Cancer Immunol Immunother. 2013 Sep 29.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00262-013-1478-7](#)

**AUTORES / AUTHORS:** - Shi RR; Liu J; Zou Z; Qi YM; Zhai MX; Zhai WJ; Gao YF

**INSTITUCIÓN / INSTITUTION:** - Department of Bioengineering, Zhengzhou University, 100 Science Road, Zhengzhou, 450001, Henan Province, People's Republic of China.

**RESUMEN / SUMMARY:** - PIWIL2, a member of PIWI/AGO family, is expressed in germline stem cells and precancerous stem cells, but not in adult somatic cells. PIWIL2 plays an important role in tumor development. It is considered as a cancer-testis antigen (CT80). It has been reported that the spliced fragment of PIWIL2, PL2L60, was widely expressed in cancer cell lines. In this study, HLA-A2-restricted epitopes from PL2L60 were predicted by online tools. To improve the activity of the native epitope, a candidate peptide P281 with potent binding affinity was chosen to investigate the modification strategy. A series of aromatic amino acids were introduced to substitute the first residue of P281. Then, we tested the binding affinity and stability of the peptide analogs and their ability to elicit specific immune responses both in vitro and in vivo. Our results indicated that the cytotoxic T lymphocytes (CTLs) induced by [4-CI-Phe1]P281 could elicit more potent activities than that of P281 and other analogs.

The CTLs induced by this analog could lyse target cells in HLA-A2-restricted and antigen-specific manners. [4-Cl-Phe1]P281 also showed the best resistance against degradation in human serum. In conclusion, the introduction of the unnatural amino acid, 4-Cl-Phe, into the first position could enhance the activity of the native epitope to induce cytotoxic T lymphocytes. It might be a good strategy to modify other promising native epitopes. The novel epitopes identified in this study could be used as novel candidates to the immunotherapy of HLA-A2 positive patients with tumors expressing PL2L60.

[608]

**TÍTULO / TITLE:** - Two mechanisms of tumor selective delivery of N-(2-hydroxypropyl)methacrylamide copolymer conjugated with pirarubicin via an acid-cleavable linkage.

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

**REVISTA / JOURNAL:** - J Control Release. 2013 Nov 21. pii: S0168-3659(13)00900-0. doi: 10.1016/j.jconrel.2013.11.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.jconrel.2013.11.011](#)

**AUTORES / AUTHORS:** - Nakamura H; Etrych T; Chytil P; Ohkubo M; Fang J; Ulbrich K; Maeda H

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Microbiology and Oncology, Faculty of Pharmaceutical Sciences, Sojo University, Ikeda 4-22-1, Nishi-ku, Kumamoto 860-0082, Japan; Research Institute for Drug Delivery System, Faculty of Pharmaceutical Sciences, Sojo University, Ikeda 4-22-1, Nishi-ku, Kumamoto 860-0082, Japan.

**RESUMEN / SUMMARY:** - N-(2-Hydroxypropyl)methacrylamide copolymer containing hydrazide groups (PHPMA) conjugated with pirarubicin (THP) via a hydrazone bond (PHPMA-hyd-THP) is a drug conjugate that releases THP in the acidic milieu of a tumor. PHPMA-hyd-THP has an apparent Mw of 40,000 and a hydrodynamic diameter of 8.2+/-1.7nm but no apparent plasma protein binding. PHPMA-hyd-THP possesses two mechanisms of selectivity toward solid tumors and has potent antitumor action. The first one is drug accumulation in tumors that depends on the enhanced permeability and retention (EPR) effect, which results in a 4-20 times higher concentration of drug in the tumor than in normal tissues such as the heart, lung, and intestine. This accumulation in tumor tissue is in great contrast to that of conventional low-Mw THP. The second one is pH-dependent release of drug from PHPMA-hyd-THP: this conjugate released free THP more efficiently at a lower pH, which exists in tumors, and exerts cytotoxic activity. Free THP is known for its much faster uptake into tumor cells compared with doxorubicin. Thus, in our in vitro study, PHPMA-hyd-THP showed a higher cytotoxicity at the lower pH of tumor tissue than at the neutral pH of normal tissue. Furthermore, much more THP was liberated from the conjugate in acidic tumor tissue than in normal tissue. The EPR effect-dependent accumulation of PHPMA-hyd-THP and tumor-selective THP release in the tumor tissues led to highly tumor-selective drug accumulation, which continued for more than 72h, whereas the lowest free drug concentration was detected in normal tissues at 24h and no longer at a later time. In conclusion, we determined in our study here that the acid-cleavable PHPMA-hyd-THP conjugate had an excellent antitumor effect without appreciable adverse effects.

[609]

**TÍTULO / TITLE:** - Synthesis and antiproliferative activity of quinolone nucleosides against the human myelogenous leukemia k-562 cell line.

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

**REVISTA / JOURNAL:** - Arch Pharm (Weinheim). 2013 Oct;346(10):757-65. doi: 10.1002/ardp.201300232. Epub 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1002/ardp.201300232](#)

**AUTORES / AUTHORS:** - Wicke L; Engels JW; Gambari R; Saab AM

**INSTITUCIÓN / INSTITUTION:** - Johann Wolfgang Goethe-Universität, Institute of Organic Chemistry and Chemical Biology, Frankfurt am Main, Germany.

**RESUMEN / SUMMARY:** - A set of 6-substituted quinolone nucleosides linked to aniline or phenol via N or O heteroatom-bridges presenting new compounds were synthesized by palladium-catalyzed Buchwald-Hartwig cross-coupling reactions. 6-Bromoquinolone nucleoside precursors, being protected by either benzoyl or TBDMS protecting groups on the ribose moiety, were subjected to different Buchwald-Hartwig conditions as the key step. Defined deprotection steps led, in good yields, to the final target compounds that carry, in position 3, either ester, acid, or amide functions. Thus, a series of novel quinolone nucleoside derivatives was obtained via a convergent synthesis route. Biological tests in human chronic myelogenous leukemia K562 cells exerted an efficient antiproliferative activity for two of them without induction of differentiation. These novel nucleosides deserve further experiments to determine their antiproliferative effects on other CML cell lines.

[610]

**TÍTULO / TITLE:** - Nodule size is an independent predictor of malignancy in mutation-negative nodules with follicular lesion of undetermined significance cytology.

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

**REVISTA / JOURNAL:** - Surgery. 2013 Oct;154(4):730-6; discussion 736-8. doi: 10.1016/j.surg.2013.05.015.

●● Enlace al texto completo (gratis o de pago) [1016/j.surg.2013.05.015](#)

**AUTORES / AUTHORS:** - Mehta RS; Carty SE; Ohori NP; Hodak SP; Coyne C; LeBeau SO; Tublin ME; Stang MT; Johnson JT; McCoy KL; Nikiforova MN; Nikiforov YE; Yip L

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, University of Pittsburgh, Pittsburgh, PA.

**RESUMEN / SUMMARY:** - BACKGROUND: In thyroid nodule fine-needle aspiration (FNA) cytology, the atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) category has a 5-15% malignancy risk that increases to 85-99% when mutation testing for BRAF, RAS, RET/PTC, or PAX8/PPARGgamma is positive. However, negative testing does not exclude malignancy. The study objective was to identify clinical and imaging features that predict cancer in mutation-negative AUS/FLUS thyroid nodules. METHODS: All patients were reviewed (April 2007 to April 2009) who had AUS/FLUS cytology, negative prospective molecular testing of FNA, and histopathology. RESULTS: Of the 230 nodules, 12 (5.2%) were malignant in 11 of 190 patients, and known clinical risk factors for thyroid cancer did not predict malignancy. On preoperative imaging,  $\geq 1$  suspicious ultrasound feature was identified in 33% of nodules and occurred regardless

of histology (P = .23). Malignant mutation-negative AUS/FLUS nodules were larger than benign nodules (mean maximum diameter, 33.6 vs 24.0 mm; P = .007). On multivariate analysis, nodule size remained an independent predictor of malignancy (odds ratio, 1.043; P = .018). We observed no malignancies in 88 mutation-negative AUS/FLUS nodules <18.5 mm. CONCLUSION: Size is an independent predictor of malignancy in mutation-negative AUS/FLUS nodules and the risk increased 4.3% with every millimeter increase in nodule size. Selected patients with small, mutation-negative AUS/FLUS thyroid nodules may be managed with ultrasound surveillance in lieu of thyroidectomy.

[611]

**TÍTULO / TITLE:** - Axitinib, a selective inhibitor of vascular endothelial growth factor receptor, exerts an anticancer effect in melanoma through promoting antitumor immunity.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Oct 16.

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

[1097/CAD.0000000000000033](#)

**AUTORES / AUTHORS:** - Zhang X; Fang X; Gao Z; Chen W; Tao F; Cai P; Yuan H; Shu Y; Xu Q; Sun Y; Gu Y

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Clinical Oncology, The First Affiliated Hospital with Nanjing Medical University bState Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing, China.

**RESUMEN / SUMMARY:** - In this study, we investigated the antitumor activity of axitinib, a selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases, against melanoma cells. Axitinib dose-dependently inhibited the proliferation and induced the apoptosis of B16F1 cells in vitro. In a mouse model of melanoma xenograft, axitinib significantly suppressed tumor growth and induced apoptosis of cells in tumor tissues at a dose of 25 mg/kg. In addition, axitinib suppressed the lung metastasis of melanoma cells and prolonged the life span of tumor-bearing mice. Axitinib also enhanced the proportion of CD8 T cells and reduced the proportion of myeloid-derived suppressor cells in CD45.2 cells, whereas the proportions of CD4 T cells and Treg cells were not affected. The mRNA expressions of inducible nitric oxide synthases-2 and arginase-1, which were associated with the function of myeloid-derived suppressor cells in tumor tissues, were inhibited by axitinib. Moreover, axitinib suppressed the expressions of proinflammatory cytokines such as IL-6, TNF-alpha, and IFN-gamma. Altogether, our results showed the unique antitumor mechanism of axitinib and provided useful information for its clinical application.

[612]

**TÍTULO / TITLE:** - Serum tissue polypeptide-specific antigen is an independent predictor in breast cancer.

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

**REVISTA / JOURNAL:** - Acta Histochem. 2013 Oct 18. pii: S0065-1281(13)00166-9. doi: 10.1016/j.acthis.2013.09.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.acthis.2013.09.001](#)

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**RESUMEN / SUMMARY:** - Tissue polypeptide-specific antigen (TPS) is a tumor proliferative marker associated with cytokeratin 18. The aim of the study was to investigate the potential relationship between the preoperative serum TPS levels and the outcome in Chinese breast cancer patients. 975 consecutive female patients, affected by invasive breast cancer under investigation from January 2005 to December 2011, had their TPS levels measured with a one-step solid phase radiometric sandwich assay detecting the M3 epitope on cytokeratin 18 fragments. The cut-off value was 80U/L. The average age diagnosed with breast cancer was 48, ranging from 23 to 71. About 19% (185) patients displayed an elevated preoperative TPS level (>80U/L) associated with older age (>45), advanced cancer stage, larger tumor size (>2cm), axillary lymph node metastasis, negative progesterone receptor status, and positive HER2 status. In addition, preoperative TPS levels were also significantly connected with recurrence ( $p<0.05$ ), particularly distant metastasis and visceral metastasis. The mean preoperative TPS level was  $68.4\pm 116.43$ U/L (range 0-1839U/L). In multivariate analysis, high preoperative TPS level was recognized as an independent prognostic factor for disease-free survival ( $p<0.001$ ) and overall survival ( $p=0.023$ ). From these results we conclude that the serum preoperative TPS level may be a valuable and independent marker for breast cancer.

[613]

**TÍTULO / TITLE:** - Bovine lactoferricin B induces apoptosis of human gastric cancer cell line AGS by inhibition of autophagy at a late stage.

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

**REVISTA / JOURNAL:** - J Dairy Sci. 2013 Dec;96(12):7511-20. doi: 10.3168/jds.2013-7285. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [3168/jds.2013-7285](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Biotechnology and Animal Science, National Ilan University, 1 Shen-Lung Road Sec.1, Ilan 26047, Taiwan, Republic of China.

**RESUMEN / SUMMARY:** - Gastric cancer is one of the most common malignant cancers, with poor prognosis and high mortality rates worldwide. Therefore, development of an effective therapeutic method without side effects is an urgent need. It has been reported that cationic antimicrobial peptides can selectively bind to negatively charged prokaryotic and cancer cell membranes and exert cytotoxicity without causing severe drug resistance. In the current study, we prepared a series of peptide fragments derived from bovine lactoferrin and evaluated their anticancer potency toward the gastric cancer cell line AGS. Cell viability assay revealed that a 25-AA peptide fragment, lactoferricin B25 (LFcinB25), exhibited the most potent anticancer capability against AGS cells. Lactoferricin B25 selectively inhibited AGS cell growth in a dose-dependent manner, exhibiting a half-maximal inhibitory concentration (IC<sub>50</sub>) value of 64μM. Flow cytometry showed a notable increment of the sub-G1 populations of the cell cycle, indicating the induction of apoptosis by LFcinB25. Western blot analysis further revealed that upon LFcinB25 treatment for 2 to 6h,

apoptosis-related caspases-3, 7, 8, 9, and poly(ADP-ribose) polymerase (PARP) were cleaved and activated, whereas autophagy-related LC3-II and beclin-1 were concomitantly increased. Thus, both apoptosis and autophagy are involved in the early stage of LFcInB25-induced cell death of AGS cells. However, upon treatment with LFcInB25 for 12 to 24h, LC3-II began to decrease, whereas cleaved beclin-1 increased in a time-dependent manner, suggesting that consecutive activation of caspases cleaved beclin-1 to inhibit autophagy, thus enhancing apoptosis at the final stage. These findings provide support for future application of LFcInB25 as a potential therapeutic agent for gastric cancer.

[614]

**TÍTULO / TITLE:** - Tai Chi for Well-being of Breast Cancer Survivors With Aromatase Inhibitor-associated Arthralgias: A Feasibility Study.

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

**REVISTA / JOURNAL:** - Altern Ther Health Med. 2013 Nov-Dec;19(6):38-44.

**AUTORES / AUTHORS:** - Galantino ML; Callens ML; Cardena GJ; Piela NL; Mao JJ

**RESUMEN / SUMMARY:** - Context \* Arthralgia is common and debilitating for a significant proportion of breast cancer survivors (BCSs) and leads to poor adherence to aromatase inhibitors (AIs). Despite increased recognition of the negative impact of arthralgia on function and the poor adherence that results, very few interventions have been developed to target this side effect. Objective \* This study aimed to determine the feasibility of tai chi to improve well-being for women experiencing AI-associated arthralgias (AIAAs). Design \* The study was a pilot to (1) demonstrate the feasibility of recruitment and retention for a tai chi trial, (2) determine the safety of tai chi, and (3) identify the outcomes (function, pain, and quality of life[QOL]) that tai chi may impact. Setting \* The study took place at the Gilda's Club South Jersey in Linwood, NJ, USA. Participants \* Postmenopausal women with a history of stage I-III breast cancer reporting AIAA were enrolled. Intervention \* Group tai chi was practiced for 1 h 2 x/wk for 8 wks. Outcome Measures \* Functional outcomes included (1) sit-and-reach (SR), (2) functional reach (FR), (3) the Berg Balance Scale (BBS), and (4) timed up-and-go (TUG). The following patient-reported outcomes (PROs) were evaluated pre- and postintervention: (1) the Hospital Anxiety and Depression Scale (HADS), (2) the Functional Assessment of Cancer Therapy-Breast (FACT-B), (3) the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue), (4) the Brief Pain Inventory (BPI), (5) the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-GOG-Ntx), and (6) the Functional Assessment of Chronic Illness Therapy- Spiritual Well-being Scale (FACIT-Sp). Participants also recorded their tai chi experiences in a journal. Results \* For the 12 participants, adherence to the classes was 75%, with no adverse events reported. Participants experienced significant improvement from baseline to follow-up for the HADS anxiety (P = .003) and depression (P = .020) scales, the emotional well-being scale of the FACT-B (P = .027), the FACIT-Fatigue (P = .030), and the sit-and-teach test (P = .016). The BBS (P = .090), TUG (P = .241), BPI severity subscale (P = .058), and physical well-being subscale of the FACT-B (P = .052) showed no significant improvement. Participants reported increased relaxation, reduced stress, and enhanced sleep quality and duration. They valued the group's and the instructor's support. Conclusion \* The research team demonstrated the feasibility of a tai chi intervention for improving

wellbeing for breast cancer patients with AIAA and identified measures that may be sensitive to the impact of a tai chi intervention in this population.

[615]

**TÍTULO / TITLE:** - Predictive value of interferon-gamma release assays for postpartum active tuberculosis in HIV-1-infected women.

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

**REVISTA / JOURNAL:** - Int J Tuberc Lung Dis. 2013 Dec;17(12):1552-7. doi: 10.5588/ijtld.13.0239.

●● Enlace al texto completo (gratis o de pago) [5588/ijtld.13.0239](#)

**AUTORES / AUTHORS:** - Jonnalagadda SR; Brown E; Lohman-Payne B; Wamalwa D; Farquhar C; John-Stewart GC

**INSTITUCIÓN / INSTITUTION:** - Department of Epidemiology, University of Washington, Seattle, Washington, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Data on the prognostic utility of interferon-gamma release assays (IGRAs) for active tuberculosis (TB) among human immunodeficiency virus 1 (HIV-1) infected individuals are limited. METHODS: Samples from a perinatal cohort of HIV-1-infected women in Kenya, obtained during pregnancy, were tested using T-SPOT®.TB IGRAs to detect Mycobacterium tuberculosis-specific interferon-gamma (IFN-gamma) responses. IFN-gamma (cut-off values of >0, >=6 and >=10 spot-forming cells [SFC]/well) and CD4 cell count (cut-off values of <250 and <350 cells/l) were evaluated to determine sensitivity and specificity using a time-dependent receiver operating characteristic curve and positive predictive value (PPV) using the Kaplan Meier method for future TB within 1 year postpartum. RESULTS: Of 327 women, 9 developed TB within 1 year postpartum (incidence rate 3.5/100 person-years of follow-up, 95%CI 1.66.7). IFN-gamma >= 6 SFC/well was associated with an optimal trade-off between sensitivity (78%) and specificity (55%) and a PPV of 5.9%. In women with CD4 cell count of <250 cells/mul, the sensitivity and specificity of IFN- 6 SFC/well were respectively 89% and 63%, and the PPV was 19.2%. CONCLUSION: Among HIV-1 infected women, IFN-gamma response (>=6 SFC/well) during pregnancy lacked a high PPV for postpartum TB, but had higher sensitivity and PPV among immunosuppressed women (CD4 cell count of <250 cells/mul).

[616]

**TÍTULO / TITLE:** - Prognostic implications of radioiodine avidity and serum thyroglobulin in differentiated thyroid carcinoma with distant metastasis.

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

**REVISTA / JOURNAL:** - World J Surg. 2013 Dec;37(12):2845-52. doi: 10.1007/s00268-013-2213-4.

●● Enlace al texto completo (gratis o de pago) [1007/s00268-013-2213-4](#)

**AUTORES / AUTHORS:** - Kim HJ; Lee JI; Kim NK; Min YK; Kim SW; Chung JH

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**RESUMEN / SUMMARY:** - BACKGROUND: Although differentiated thyroid carcinoma (DTC) rarely develops distant metastases, the present study was performed to

evaluate factors that affect the survival of patients with DTC who present with distant metastasis. METHODS: Among 4,989 patients who underwent thyroid surgery for DTC, 82 presenting with distant metastasis were analyzed. Based on radioiodine ((131)I) avidity and the thyroid-stimulating hormone-stimulated serum thyroglobulin (sTg) level at the time of metastasis, patients were divided into three groups: group 1 ((131)I uptake + sTg  $\leq$  215 ng/mL, n = 46), group 2 ((131)I uptake + sTg > 215 ng/mL, n = 24), group 3 (no (131)I uptake, n = 12). Disease-specific survival (DSS) was estimated using the Kaplan-Meier method. Factors predicting the outcome were evaluated using Cox proportional hazard regression analysis. RESULTS: The age of patients (p = 0.04), frequency of follicular thyroid carcinoma (p = 0.002), tumor size (p < 0.001), and number of multiple metastatic sites (p = 0.004) differed significantly among the groups. With a median follow-up after surgery of 72 months, the 5- and 10-year DSSs for all patients were 84 and 69 %, respectively. The predictors of survival were age (p = 0.004), symptoms at the time of presentation (p = 0.045), histology (p = 0.01), sites of metastasis (p = 0.03), and (131)I avidity and sTg level at the time of metastasis (p = 0.002). In the multivariate analysis, age, histology, and (131)I avidity and sTg level at the time of metastasis remained significant factors for survival. CONCLUSIONS: Certain DTC patients with distant metastasis demonstrate favorable outcomes dependent on age, histology, and (131)I avidity and sTg level at the time of metastasis.

[617]

**TÍTULO / TITLE:** - The prognostic significance of the BRAFV600E mutation in papillary thyroid carcinoma detected by mutation-specific immunohistochemistry.

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

**REVISTA / JOURNAL:** - Pathology. 2013 Dec;45(7):637-44. doi: 10.1097/PAT.0000000000000008.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1097/PAT.0000000000000008](#)

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**INSTITUCIÓN / INSTITUTION:** - \*Departments of Anatomical Pathology daggerSurgery, St Vincent's Hospital, Melbourne double daggerDepartment of Pathology, University of Melbourne, Melbourne, Victoria, Australia; double daggerthese authors contributed equally.

**RESUMEN / SUMMARY:** - AIMS: BRAF mutation has been shown in a large meta-analysis to be an independent prognostic marker for papillary thyroid carcinoma (PTC) with poorer survival and higher recurrence rates. METHODS: We studied prevalence of BRAF mutation in 77 patients with PTC from an Australian cohort using competitive polymerase chain reaction (C-PCR) and immunohistochemistry (IHC) with BRAF-specific antibody, VE1. Clinicopathological parameters, recurrence and mortality were analysed according to BRAF mutation status. RESULTS: Median follow-up was 84.5 months. BRAF mutation was demonstrated in 65% of cases combining both C-PCR and IHC; in 71% (37/77) of tumours >1 cm and 52% (13/25) of microcarcinomas (<1 cm). IHC was positive in 69% (49/71) and C-PCR in 53% (41/77); 87% (67/77) of our patients were treated with total thyroidectomy and 65% (50/77) also had radioactive ablation. BRAF positive tumours had a significantly higher rate of subsequent lymph node metastases (p = 0.035). Significant association was found between BRAF

mutation and male sex ( $p = 0.034$ ), but not between age  $>45$  years at diagnosis, size of primary tumour, extrathyroidal extension, lymph node or distant metastases or clinical stage at diagnosis. CONCLUSIONS: BRAF mutation in PTC determined by IHC is associated with significantly increased risk of lymph node recurrence.

[618]

**TÍTULO / TITLE:** - Peripheral blood absolute lymphocyte/monocyte ratio as a useful prognostic factor in diffuse B-cell lymphoma in the rituximab era.

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

**REVISTA / JOURNAL:** - Eur J Haematol. 2013 Oct 25. doi: 10.1111/ejh.12221.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ejh.12221](#)

**AUTORES / AUTHORS:** - Watanabe R; Tomita N; Itabashi M; Ishibashi D; Yamamoto E; Koyama S; Miyashita K; Takahashi H; Nakajima Y; Hattori Y; Motohashi K; Takasaki H; Ohshima R; Hashimoto C; Yamazaki E; Fujimaki K; Sakai R; Fujisawa S; Motomura S; Ishigatsubo Y

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**RESUMEN / SUMMARY:** - OBJECTIVES: The tumor microenvironment, including tumor-infiltrating lymphocytes and myeloid-derived cells, is an important factor in the pathogenesis and clinical behavior of malignant lymphoma. However, the prognostic significance of peripheral lymphocytes and monocytes in lymphoma remains unclear. METHODS: We evaluated the prognostic impact of the absolute lymphocyte count (ALC), absolute monocyte count (AMC), and lymphocyte/monocyte ratio (LMR) in 359 diffuse large B-cell lymphoma (DLBCL) patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). RESULTS: The median follow-up time of the surviving patients was 58 months. Low ALC and an elevated AMC were both associated with poor survival rates. Receiver operating characteristic curve analysis showed that LMR was the best predictor of survival, with 4.0 as the cutoff point. Patients with  $LMR \leq 4.0$  were more likely to have an aggressive tumor, and this was associated with poor treatment responses. Patients with  $LMR \leq 4.0$  at diagnosis had significantly poorer overall survival (OS) and progression-free survival (PFS) than those with  $LMR > 4.0$ . Multivariate analysis, which included prognostic factors of the International Prognostic Index, showed  $LMR \leq 4.0$  to be an independent predictor for the OS (hazard ratio [HR], 2.507; 95% confidence interval [CI], 1.255-5.007;  $P = 0.009$ ) and PFS (HR, 2.063; 95% CI, 1.249-3.408;  $P = 0.005$ ). CONCLUSIONS: The LMR at diagnosis, as a simple index which reflects host systemic immunity, predicts clinical outcomes in DLBCL patients treated with R-CHOP.

[619]

**TÍTULO / TITLE:** - Debulking surgery followed by intraarterial 5-fluorouracil chemotherapy plus subcutaneous interferon alfa for massive hepatocellular carcinoma with multiple intrahepatic metastases: A pilot study.

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

**REVISTA / JOURNAL:** - Eur J Surg Oncol. 2013 Dec;39(12):1364-70. doi: 10.1016/j.ejso.2013.10.007. Epub 2013 Oct 23.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejso.2013.10.007](https://doi.org/10.1016/j.ejso.2013.10.007)

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**RESUMEN / SUMMARY:** - BACKGROUND: The prognosis in advanced hepatocellular carcinoma (HCC) with multiple intrahepatic metastases is extremely poor. Combination therapy with subcutaneous interferon (IFN) alfa and intraarterial 5-fluorouracil was reported to be effective against such advanced HCC. We describe results of debulking surgery followed by combination therapy with IFN alfa and 5-FU for massive HCC with multiple intrahepatic metastases. METHODS: In 27 HCC patients with massive tumors and multiple intrahepatic metastases, we performed combination therapy with IFN alfa and 5-FU after maximal liver tumor resection. RESULTS: Mean patient age was 63.3 years. Including intrahepatic metastases, tumors numbered 5 or more in 17 patients (63%). Portal or hepatic vein branches were invaded in 22 (81%). The mean maximum tumor diameter was 102 mm. Among 24 patients whose results were analyzed, an objective response by residual intrahepatic metastases was observed in 13 (54%; complete response in 12, and partial response in 1). Overall 1-, 3-, and 5-year survival was 73.2%, 38.7%, and 38.7%, respectively; 1-, 3-, and 5-year progression-free rates were 38.2%, 22.3%, and 22.3%. CONCLUSIONS: Debulking surgery followed by IFN alfa and 5-FU combination chemotherapy offers possibility of long-term survival despite massive HCC with multiple intrahepatic metastases.

[620]

**TÍTULO / TITLE:** - Osteopontin Combined With CD44v6, a Novel Prognostic Biomarker in Non-Small Cell Lung Cancer Undergoing Curative Resection.

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

**REVISTA / JOURNAL:** - Ann Thorac Surg. 2013 Dec;96(6):1943-51. doi: 10.1016/j.athoracsur.2013.07.089. Epub 2013 Oct 3.

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

[1016/j.athoracsur.2013.07.089](https://doi.org/10.1016/j.athoracsur.2013.07.089)

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**INSTITUCIÓN / INSTITUTION:** - Department of Lung Cancer, Tianjin Cancer Institute and Hospital, Tianjin Medical University, Tianjin Lung Cancer Center, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Osteopontin (OPN) is identified as one of the leading genes that promote the metastasis of malignant tumor through binding to CD44v6 and integrin. The purpose of the current study was to assess the prognostic significance of OPN and CD44v6 in patients with non-small cell lung cancer (NSCLC). METHODS: Tissue microarray was used to detect the expression of OPN and CD44v6 in 159 NSCLC patients undergoing complete pulmonary resection in our hospital between 2003 and 2006. The correlations among OPN, CD44v6, and clinicopathologic data were analyzed using chi(2) testing analysis. The prognostic values of OPN and CD44v6 were evaluated by univariate Kaplan-Meier survival analysis and multivariate Cox proportional hazard model analysis. RESULTS: OPN and CD44v6 were both independent predictors for overall survival and disease-free survival. When OPN and

CD44v6 were considered together, the predictive range was extended and the sensitivity was improved, especially for those patients with stage I NSCLC. The 6-year overall survival and disease-free survival rates in OPN+ or CD44v6+ patients were 49.1% and 39.6%, respectively, which were significantly lower than those of OPN-/CD44v6- patients (64.4% and 47.7%, respectively), and were higher than those of OPN+/CD44v6+ patients (16.4% and 14.8%, respectively). Stratification into OPN+/CD44v6+, OPN+ or CD44v6+, or OPN-/CD44v6- groups, based on the expression OPN and CD44v6, could efficiently predicted outcomes ( $p < 0.001$ ) of NSCLC patients. CONCLUSIONS: The combination of OPN and CD44v6 is a valuable independent predictor of tumor recurrence and survival in NSCLC patients.

[621]

**TÍTULO / TITLE:** - Multifunctional Tumor-Targeting Nanocarriers Based on Hyaluronic Acid-Mediated and pH-Sensitive Properties for Efficient Delivery of Docetaxel.

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

**REVISTA / JOURNAL:** - Pharm Res. 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [1007/s11095-013-1225-y](#)

**AUTORES / AUTHORS:** - Song S; Chen F; Qi H; Li F; Xin T; Xu J; Ye T; Sheng N; Yang X; Pan W

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, PO Box No. 122, 103 Wenhua Rd., Shenyang, 110016, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: The objective of this work was to develop a multifunctional tumor-targeting nanocarrier based on the mechanism of CD44-mediated endocytosis and pH-induced drug release to improve the therapeutic efficacy of docetaxel (DTX). METHODS: Hyaluronic acid-coated docetaxel-loaded cholesteryl hemisuccinate vesicles (HA-CHEMS vesicles) were prepared. The physicochemical properties and pH-dependent drug release of HA-CHEMS vesicles were evaluated. The HA-CHEMS vesicles were investigated for CD44-mediated internalization and in vitro cell viability using MCF-7, A549 and L929 cells. In addition, tissue distribution as well as antitumor efficacy was also evaluated in MCF-7 tumor-bearing mouse model. RESULTS: The particle size and zeta potential of HA-CHEMS vesicles were 131.4 +/- 6.2 nm and -13.3 +/- 0.04 mV, respectively. The in vitro drug release results demonstrated a pH-responsive drug release under different pH conditions. In vitro cell viability tests suggested that the encapsulation of DTX in HA-CHEMS vesicles led to more than 51.6-fold and 46.3-fold improved growth inhibition in MCF-7 and A549 cell lines, respectively compared to Taxotere®. From the cell uptake studies, the coumarin 6-loaded HA-CHEMS vesicles enhanced intracellular fluorescent intensity in the CD44-overexpressing cell line (MCF-7). Biodistribution studies revealed selective accumulation of HA-CHEMS vesicles in the MCF-7 bearing BalB/c nude mice as a result of passive accumulation and active targeting (CD44-mediated endocytosis). Compared to Taxotere®, HA-CHEMS vesicles exhibited higher antitumor activity by reducing tumor volume ( $P < 0.05$ ) and drug toxicity, demonstrating the success of the multifunctional targeting delivery. CONCLUSIONS: This work corresponds to the preparation of a multifunctional tumor-targeted delivery system. Our investigation shows that hyaluronan-bearing docetaxel-loaded cholesteryl hemisuccinate vesicles

(HA-CHEMS vesicles) is a highly promising therapeutic system, leading to tumor regression after intravenous administration without visible toxicity.

[622]

**TÍTULO / TITLE:** - Pleural effusion hyaluronic acid as a prognostic marker in pleural malignant mesothelioma.

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

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Dec;82(3):491-8. doi: 10.1016/j.lungcan.2013.09.016. Epub 2013 Oct 9.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.09.016](#)

**AUTORES / AUTHORS:** - Creaney J; Dick IM; Segal A; Musk AW; Robinson BW

**INSTITUCIÓN / INSTITUTION:** - National Centre for Asbestos Related Diseases, University of Western Australia, School of Medicine and Pharmacology, Nedlands, Western Australia, Australia; The Australian Mesothelioma Tissue Bank, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia. Electronic address: [jenette.creaney@uwa.edu.au](mailto:jenette.creaney@uwa.edu.au).

**RESUMEN / SUMMARY:** - BACKGROUND: Malignant mesothelioma (MM), a primarily asbestos-induced tumour, has a poor prognosis, with over-all 5-year survival less than 5%. Tumour biomarkers are being intensely investigated in MM as aids to diagnosis and prognosis. Hyaluronic acid (HA) is produced in MM but its role in prognostication remains uncertain. MATERIALS AND METHODS: HA concentrations were determined in matching serum and pleural effusion of 96 MM patients, 26 lung cancer patients and 42 patients with benign effusions resulting from infectious, cardiac, renal, liver and rheumatoid diseases and compared to the current 'best practice' biomarker, mesothelin. Liver and kidney function were determined for each patient. Diagnostic accuracy was determined by area under the receiver operator characteristic curve (AUC) analysis following logistic regression modelling. Difference in survival between groups was determined by both log-rank test and Cox proportional hazards regression modelling. RESULTS: For effusion HA, the AUC (IQ range) was 0.89 (0.82-0.94) and for effusion mesothelin, it was 0.85 (0.78-0.90). Serum HA was not diagnostically useful. A combined measure of effusion HA, and serum and effusion mesothelin had an AUC of 0.92 (0.86-0.96), which was significantly higher than effusion mesothelin alone. Effusion HA had a biphasic distribution in MM patients, dichotomised at a concentration of 75mg/L. The median survival of MM patients with high effusion HA was 18.0 (13.7-22.4) months, significantly longer than those with low HA effusion levels (12.6 months (8.4-16.8), p=0.004). Serum HA, and effusion and serum mesothelin were not significant prognostic indicators. CONCLUSION: This study demonstrates that a combined biomarker panel has greater diagnostic accuracy than effusion mesothelin alone, and that significant prognostic information is provided by effusion HA.

[623]

**TÍTULO / TITLE:** - The role of epigenetics in the regulation of apoptosis in myelodysplastic syndromes and acute myeloid leukemia.

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

**REVISTA / JOURNAL:** - Crit Rev Oncol Hematol. 2013 Oct 12. pii: S1040-8428(13)00213-8. doi: 10.1016/j.critrevonc.2013.10.003.

- Enlace al texto completo (gratis o de pago) [1016/j.critrevonc.2013.10.003](https://doi.org/10.1016/j.critrevonc.2013.10.003)

**AUTORES / AUTHORS:** - Karlic H; Herrmann H; Varga F; Thaler R; Reitermaier R; Spitzer S; Ghanim V; Blatt K; Sperr WR; Valent P; Pfeilstocker M

**INSTITUCIÓN / INSTITUTION:** - Ludwig Boltzmann Cluster Oncology, Vienna, Austria; Ludwig Boltzmann Institute for Leukemia Research and Hematology, Hanusch Hospital, Vienna, Austria. Electronic address: [heidrun.karlic@meduniwien.ac.at](mailto:heidrun.karlic@meduniwien.ac.at).

**RESUMEN / SUMMARY:** - Disordered stem cell epigenetics and apoptosis-regulating mechanisms contribute essentially to the pathogenesis of myelodysplastic syndromes (MDS) and may trigger disease-progression to secondary acute myeloid leukemia (AML). Expression of apoptosis-mediators FAS (CD95) and DAPK1 the latter being also known for its association with autophagy are upregulated in neoplastic cells in patients with low-risk MDS and epigenetically silenced and downregulated in high-risk MDS and AML as confirmed by a study 50 MDS and 30 AMLs complementing this review. 5-Azacytidine (AZA) and 5-aza-2'-deoxycytidine (DAC), promoted FAS and DAPK1 gene demethylation and their (re)expression as well as apoptosis in leukemic cell lines (HL-60, KG1) which can be reversed by siRNA against FAS. Thus, promoter-demethylation of FAS and DAPK1 represents a critical mechanism of drug-induced apoptosis in neoplastic cells in MDS and AML which underscores the clinical implication of epigenetically active therapies.

[624]

**TÍTULO / TITLE:** - Regorafenib: A Novel Multitargeted Tyrosine Kinase Inhibitor for Colorectal Cancer and Gastrointestinal Stromal Tumors.

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

**REVISTA / JOURNAL:** - Ann Pharmacother. 2013 Nov 1.

- Enlace al texto completo (gratis o de pago) [1177/1060028013509792](https://doi.org/10.1177/1060028013509792)

**AUTORES / AUTHORS:** - Crona DJ; Keisler MD; Walko CM

**INSTITUCIÓN / INSTITUTION:** - University of North Carolina (UNC) Eshelman School of Pharmacy, NC, USA.

**RESUMEN / SUMMARY:** - OBJECTIVE: To review currently available literature on the oral multikinase inhibitor regorafenib and its role in the treatment of metastatic colorectal cancer (mCRC), and imatinib- and sunitinib-resistant gastrointestinal stromal tumors (GISTs). DATA SOURCES: A comprehensive literature search was performed of PubMed/MEDLINE and American Society of Clinical Oncology (ASCO) abstracts (through August 2013). STUDY SELECTION/DATA EXTRACTION: Preclinical pharmacological and phase I to III trials data analyzing regorafenib efficacy and safety in mCRC or imatinib- and sunitinib-resistant GIST patients were evaluated. All available English-language, peer-reviewed articles and ASCO abstracts with relevant information were reviewed. DATA SYNTHESIS: Regorafenib was approved for mCRC in September 2012 and for imatinib- and sunitinib-resistant GISTs in February 2013. Regorafenib is an inhibitor of stromal, angiogenic, and oncogenic receptor tyrosine kinases, as well as the RAF/MEK/ERK signaling pathway. Phase III CORRECT (Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer) trial data demonstrated an overall survival benefit for mCRC patients treated with regorafenib (6.4 vs 5.0 months; P = .0052). Phase III GRID (Gastrointestinal Stromal Tumors After Failure of Imatinib and Sunitinib) trial data revealed a progression-free survival benefit in imatinib- and sunitinib-resistant GIST patients (4.8 vs 0.9 months; P

< .0001). Its adverse event (AE) profile is comparable to that of other multikinase inhibitors. The most commonly observed grade  $\geq 3$  AEs included hypertension, hand-foot skin reaction, rash, diarrhea, and fatigue. CONCLUSIONS: Regorafenib is a novel oral multikinase inhibitor that has shown promising results for patients with advanced, unresectable or metastatic treatment-refractory CRCs or imatinib- and sunitinib-resistant GISTs.

[625]

**TÍTULO / TITLE:** - MACC1 is involved in the regulation of proliferation, colony formation, invasion ability, cell cycle distribution, apoptosis and tumorigenicity by altering Akt signaling pathway in human osteosarcoma.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 27.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1335-5](#)

**AUTORES / AUTHORS:** - Zhang K; Tian F; Zhang Y; Zhu Q; Xue N; Zhu H; Wang H; Guo X

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopaedics, Chinese PLA General Hospital & Chinese PLA Medical School, No. 28 Fuxing Road, Haidian District, Beijing, 100853, China.

**RESUMEN / SUMMARY:** - There is mounting evidence that metastasis-associated in colon cancer-1 (MACC1) plays pivotal roles in development and progression of many tumors, particularly in osteosarcoma (OS). However, its precise roles and molecular mechanisms remain to be delineated in OS. In the current study, we found that the levels of MACC1 mRNA and protein in four OS cell lines (MG-63, HOS, SaOS-2 and U2OS) were significantly higher than that in hFOB1.19 osteoblast ( $P < 0.05$ ). The vector pcDNA-MACC1 contributed to the increase of MACC1 level in MG-63 cells, whereas MACC1 siRNA evoked the decrease of MACC1 level in U2OS cells. In addition, MACC1 downregulation caused the inhibition of cell proliferation in vitro, colony formation, invasion and tumor growth in vivo, arrested cell cycle in G0/G1 phase and induced cell apoptosis in U2OS cells, and reversed effects were observed in MG-63 cells by MACC1 upregulation. Most notably, MACC1 depletion markedly inactivated Akt signaling pathway in U2OS cells, conversely, MACC1 upregulation evidently activated Akt signaling pathway in MG-63 cells. Collectively, our data presented herein suggest that biological implications triggered by MACC1 may be tightly associated with the status of Akt signaling pathway in OS.

[626]

**TÍTULO / TITLE:** - Dual ALK and EGFR inhibition targets a mechanism of acquired resistance to the tyrosine kinase inhibitor crizotinib in ALK rearranged lung cancer.

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

**REVISTA / JOURNAL:** - Lung Cancer. 2013 Oct 14. pii: S0169-5002(13)00448-0. doi: 10.1016/j.lungcan.2013.09.019.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.09.019](#)

**AUTORES / AUTHORS:** - Yamaguchi N; Lucena-Araujo AR; Nakayama S; de Figueiredo-Pontes LL; Gonzalez DA; Yasuda H; Kobayashi S; Costa DB

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.

**RESUMEN / SUMMARY:** - INTRODUCTION: The multitargeted tyrosine kinase inhibitor (TKI) crizotinib is active against ALK translocated non-small-cell lung cancer (NSCLC); however acquired resistance invariably develops over time. ALK mutations have previously been implicated in only a third of resistant tumors. We sought to evaluate alternative mechanisms of resistance and preclinical strategies to overcome these in a cell line driven by EML4-ALK. METHODS: We selected the NSCLC cell line NCI-H3122 (H3122: EML4-ALK E13;A20) and derived resistant variants that were able to grow in the presence of 1µM crizotinib. These were analyzed for ALK mutations, sensitivity to crizotinib in combination with other TKIs, and for activation of alternative tyrosine kinases. RESULTS: All H3122 crizotinib resistant (CR) clones lacked amplification or mutations in the kinase domain of ALK. To evaluate if possible alternative kinases functioned as “bypass” tracks for downstream signaling activation in these resistance cells, we performed a phospho-receptor tyrosine kinase array that demonstrated that CR clones had higher phospho-EGFR signals than H3122 cells before and after exposure to crizotinib. A functional approach of dual ALK TKI (with crizotinib) with combinatory TKI inhibition was used as a secondary screen for possible targets. Crizotinib+erlotinib (reversible EGFR TKI) and crizotinib+afatinib (irreversible EGFR/ERBB2 TKI) were able to inhibit the growth of H3122 CR clones, confirming EGFR activation as a mechanism of resistance. The removal of crizotinib from the culture media re-sensitized CR cells to crizotinib. CONCLUSIONS: We identified activation of EGFR as a mechanism of resistance to crizotinib in preclinical models of ALK translocated NSCLC. If EGFR activation is confirmed as a predominant mechanism of ALK TKI-induced resistance in patient-derived tumors, the use of ALK plus EGFR TKIs could be explored for this important cohort of NSCLCs.

[627]

**TÍTULO / TITLE:** - TS mRNA levels can predict pemetrexed and raltitrexed sensitivity in colorectal cancer.

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

**REVISTA / JOURNAL:** - Cancer Chemother Pharmacol. 2013 Nov 27.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2354-z](#)

**AUTORES / AUTHORS:** - Zhang Q; Shen J; Wang H; Hu J; Yu L; Xie L; Wei J; Liu B; Guan W; Qian X

**INSTITUCIÓN / INSTITUTION:** - The Comprehensive Cancer Centre, Drum Tower Hospital, Medical School of Nanjing University, Clinical Cancer Institute of Nanjing University, 321 Zhongshan Rd, Nanjing, 210008, People's Republic of China.

**RESUMEN / SUMMARY:** - PURPOSE: The purpose of the study is to analyze the relationship between tumor thymidylate synthase (TS) mRNA expression levels and raltitrexed/pemetrexed/5-FU sensitivity. PATIENTS AND METHODS: We collected freshly removed colorectal tumor specimens from 50 patients. Chemosensitivities to anticancer drugs were evaluated by histoculture drug response assay. We adopted quantitative reverse transcription polymerase chain reaction for TS mRNA detection and immunohistochemical staining for assessing TS expression in tumor tissues. RESULTS: There is a significant relationship between TS mRNA expression levels and

in vitro chemosensitivity of freshly removed colorectal tumor specimens to pemetrexed ( $P < 0.001$ )/raltitrexed ( $P = 0.004$ )/5-FU ( $P = 0.007$ ). CONCLUSIONS: TS mRNA expression levels can predict pemetrexed and raltitrexed sensitivity in colorectal cancer.

[628]

**TÍTULO / TITLE:** - In vitro modulation of MMP-2 and MMP-9 in pediatric human sarcoma cell lines by cytokines, inducers and inhibitors.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):27-34. doi: 10.3892/ijo.2013.2159. Epub 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2159](#)

**AUTORES / AUTHORS:** - Roomi MW; Kalinovskiy T; Rath M; Niedzwiecki A

**INSTITUCIÓN / INSTITUTION:** - Dr Rath Research Institute, Santa Clara, CA 95050, USA.

**RESUMEN / SUMMARY:** - The highly aggressive pediatric sarcomas are characterized by high levels of matrix metalloproteinase (MMP)-2 and MMP-9, which play crucial roles in tumor invasion and metastasis by degradation of the extracellular membrane leading to cancer cell spread to distal organs. We examined the effects of cytokines, mitogens, inducers and inhibitors on MMP-2 and -9 expression in osteosarcoma (U2OS) and rhabdomyosarcoma (RD). The selected compounds included natural cytokines and growth factors, as well as chemical compounds applied in therapy of sarcoma and natural compounds that have demonstrated anticancer therapeutic potential. These cell lines were cultured in their respective media to near confluence and the cells were washed with PBS and incubated in serum-free medium with various concentrations of several cytokines, mitogens and inhibitors. After 24 h the media were removed and analyzed for MMP-2 and -9 by gelatinase zymography and quantitated by densitometry. Osteosarcoma and rhabdomyosarcoma showed bands corresponding to MMP-2 and -9 with dose-dependent enhancement of MMP-9 with phorbol 12-myristate 13-acetate (PMA) treatment. Tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$  and LPS enhanced osteosarcoma U2OS MMP-9 secretion but had no effect on MMP-2 secretion. Tumor necrosis factor- $\alpha$  stimulated rhabdomyosarcoma MMP-2 expression, but had no effect on MMP-9 secretion. Doxycycline, epigallocatechin gallate, nutrient mixture (NM), actinomycin-D, cyclohexamide, retinoic acid and dexamethasone inhibited MMP-2 and -9 in U2OS osteosarcoma cells. PMA-treated RD cells showed dose-response inhibition of MMP-9 by doxycycline and epigallocatechin gallate and both MMPs by NM. Dexamethasone and actinomycin-D showed inhibition of MMP-2 secretion of RD cells. Our results show that cytokines, mitogens and inducers show variable upregulation of U2OS osteosarcoma and RD rhabdomyosarcoma MMP-2 and -9 secretion, and inhibitors demonstrate downregulation under stimulatory conditions, suggesting the application of these agents for the development of effective therapies in pediatric sarcomas.

[629]

**TÍTULO / TITLE:** - Harmine induces apoptosis and inhibits tumor cell proliferation, migration and invasion through down-regulation of cyclooxygenase-2 expression in gastric cancer.

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

**REVISTA / JOURNAL:** - Phytomedicine. 2013 Oct 28. pii: S0944-7113(13)00364-4. doi: 10.1016/j.phymed.2013.09.007.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.phymed.2013.09.007](#)

**AUTORES / AUTHORS:** - Zhang H; Sun K; Ding J; Xu H; Zhu L; Zhang K; Li X; Sun W

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatric Gastroenterology, the First Affiliated Hospital to Nanjing Medical University, Nanjing 210029, PR China.

**RESUMEN / SUMMARY:** - Cyclooxygenase-2 (COX-2) plays an important role in the carcinogenesis and progression of gastric cancer. Harmine is reported as a promising drug candidate for cancer therapy; however, effects and action mechanism of harmine on the human gastric cancer cells remain unclear. This study evaluated the anti-tumor effects of harmine on human gastric cancer both in vitro and in vivo. The cell proliferation was determined using MTT colorimetric assay. Apoptosis was measured by DAPI staining and flow cytometry analysis. The wound healing and transwell invasion assays were performed to evaluate the effects of harmine on the migration and invasion of gastric cancer cells. The expression of COX-2, proliferating cell nuclear antigen (PCNA), Bcl-2, Bax and matrix metalloproteinase-2 (MMP-2) was detected by Western blot analysis. Our results showed that harmine significantly inhibited cellular proliferation, migration, invasion and induced apoptosis in vitro, as well as inhibited tumor growth in vivo. In addition, harmine significantly inhibited the expression of COX-2, PCNA, Bcl-2 and MMP-2 as well as increased Bax expression in gastric cancer cells. These results collectively indicate that harmine induces apoptosis and inhibits proliferation, migration and invasion of human gastric cancer cells, which may be mediated by down-regulation of COX-2 expression.

[630]

**TÍTULO / TITLE:** - A9 Region in EPHB2 Mutation Is Frequent in Tumors with Microsatellite Instability. Analysis of Prognosis.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Nov;33(11):5159-63.

**AUTORES / AUTHORS:** - Rafael S; Vidaurreta M; Veganzones S; DE LA Orden V; Mediero B; Gutierrez ML; Maestro ML

**INSTITUCIÓN / INSTITUTION:** - Department of Genomics, Hospital Clinico San Carlos. c/Martin Lagos s/n, 28040 Madrid, España. [sara.rafael.f@gmail.com](mailto:sara.rafael.f@gmail.com).

**RESUMEN / SUMMARY:** - Aim: The aim of the present study was to determine the relation of EPH tyrosine kinase receptor B2 (EPHB2) A9 region mutation and microsatellite instability (MSI); and to analyze their influence in prognosis of patients with sporadic colorectal cancer (CRC). PATIENTS AND METHODS: A total of 481 patients with CRC were examined. MSI (NCI criteria) and EPHB2 were analyzed using PCR and fragment analysis software. RESULTS: EPHB2 mutation was detected in 3.1% of patients. Mutation of EPHB2 was associated with location and with MSI status. We considered low instability (L-MSI) when only one marker showed instability, high instability (H-MSI) when two or more markers were positive and microsatellite stable (MSS) when no instability was detected. The stratified analysis of overall survival (OS)

and disease-free survival (DFS) in MSI according to EPHB2 status revealed no statistically significant differences. However, the risk of recurrence of H-MSI tumors with EPHB2 mutation carriers was 3.6-times higher than in non-mutation carriers. CONCLUSION: The frequency of EPHB2 mutation is higher in patients with H-MSI than MSS tumors. Promising results were found regarding the prognostic influence of EPHB2 in H-MSI.

[631]

**TÍTULO / TITLE:** - The long non-coding RNA HOTAIR is upregulated in endometrial carcinoma and correlates with poor prognosis.

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

**REVISTA / JOURNAL:** - Int J Mol Med. 2013 Nov 27. doi: 10.3892/ijmm.2013.1570.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1570](#)

**AUTORES / AUTHORS:** - He X; Bao W; Li X; Chen Z; Che Q; Wang H; Wan XP

**INSTITUCIÓN / INSTITUTION:** - International Peace Maternity and Child Health Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200030, P.R. China.

**RESUMEN / SUMMARY:** - Long non-coding RNAs (lncRNAs) are emerging as key molecules in human cancer. Homeobox (HOX) transcript antisense intergenic RNA (HOTAIR), a long non-coding RNA (lncRNA), is associated with a variety of human cancers, such as breast, liver and lung cancer. However, whether HOTAIR can function as a molecular marker in endometrial carcinoma (EC) remains unknown. In the present study, the expression of HOTAIR in 66 EC tissues from patients with EC and 30 normal tissues from healthy age-matched control subjects was determined using quantitative reverse transcription PCR. Furthermore, using in situ hybridization, we measured HOTAIR expression in 129 formalin-fixed paraffin-embedded (FFPE) tissue sections, which included 96 tissues that matched the frozen cases, 21 other EC tissues and 12 atypical hyperplasia tissues. Correlations between HOTAIR expression and the clinicopathological characteristics of patients were analyzed. Our results revealed that HOTAIR expression in the EC tissues was significantly upregulated compared with normal tissues ( $p < 0.001$ ). In addition, we observed a significant association between HOTAIR expression and the EC grade ( $p < 0.05$ ) and lymph node metastasis ( $p < 0.05$ ). Moreover, in the FFPE tissues, but not the frozen tissues, we found that a higher HOTAIR expression also correlated with the depth of myometrial invasion ( $p = 0.019$ ) and lymphovascular space invasion ( $p = 0.015$ ). More importantly, patients with a higher HOTAIR expression showed significantly poorer overall survival than those with lower HOTAIR expression ( $p < 0.05$ ). In conclusion, our results suggest that a high expression of HOTAIR is involved in the progression of cancer and may be a novel biomarker of poor prognosis in patients with EC.

[632]

**TÍTULO / TITLE:** - Epigenetic and expression analysis of TRAIL-R2 and BCL2: on the TRAIL to knowledge of apoptosis in ovarian tumors.

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

**REVISTA / JOURNAL:** - Arch Gynecol Obstet. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1007/s00404-013-3060-0](#)

**AUTORES / AUTHORS:** - da Conceicao Braga L; Silva LM; Piedade JB; Traiman P; da Silva Filho AL

**INSTITUCIÓN / INSTITUTION:** - Servico de Biologia Celular, Diretoria de Pesquisa e Desenvolvimento da Fundacao Ezequiel Dias, Belo Horizonte, MG, Brazil.

**RESUMEN / SUMMARY:** - OBJECTIVE: This study assesses TRAIL-R2 (TNF-related apoptosis-inducing ligand receptor 2) and BCL2 (B cell CLL/lymphoma 2) expression as well as CpG island methylation within the TRAIL-R2 promoter in ovarian serous tumors and primary and metastatic serous EOC (epithelial ovarian cancer).

METHODS: RNA and DNA were obtained from women with normal ovarian tissues (n = 18), ovarian serous cystadenoma tumors (n = 11) and serous EOC (n = 16) using Trizol®. Quantitative PCR was performed to quantify the relative levels of TRAIL-R2 and BCL2. The methylation frequency of the TRAIL-R3 promoter was assessed using a methylation-specific PCR assay after DNA bisulfite conversion. Differences between the groups were evaluated using the chi 2, Mann-Whitney U or Kruskal-Wallis tests, as indicated. RESULTS: We identified TRAIL-R2 and BCL2 mRNA expressed in all ovarian tumor groups, and there were significant differences between the groups. Both genes had low expression levels in ovarian serous cystadenoma and primary EOC tumors when compared with metastatic EOC. Methylation of the TRAIL-R2 promoter was frequently observed in all groups; however, there were no statistically significant associations. CONCLUSIONS: Primary EOC is associated with lower TRAIL-R2 and BCL2 expression levels, while metastatic EOC is associated with higher expression of these genes. Promoter DNA methylation was not related to this finding, suggesting there are other mechanisms involved in transcriptional control.

[633]

**TÍTULO / TITLE:** - In silico simulations of STAT1 and STAT3 inhibitors predict SH2 domain cross-binding specificity.

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

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 Nov 15;720(1-3):38-48. doi: 10.1016/j.ejphar.2013.10.055. Epub 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejphar.2013.10.055](#)

**AUTORES / AUTHORS:** - Szelag M; Sikorski K; Czerwoniec A; Szatkowska K; Wesoly J; Bluysen HA

**INSTITUCIÓN / INSTITUTION:** - Department of Human Molecular Genetics, Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University in Poznan, Umultowska 89, 61-614 Poznan, Poland.

**RESUMEN / SUMMARY:** - Signal transducers and activators of transcription (STATs) comprise a family of transcription factors that are structurally related and which participate in signaling pathways activated by cytokines, growth factors and pathogens. Activation of STAT proteins is mediated by the highly conserved Src homology 2 (SH2) domain, which interacts with phosphotyrosine motifs for specific contacts between STATs and receptors and for STAT dimerization. By generating new models for human (h)STAT1, hSTAT2 and hSTAT3 we applied comparative in silico docking to determine SH2-binding specificity of the STAT3 inhibitor stattic, and of fludarabine (STAT1 inhibitor). Thus, we provide evidence that by primarily targeting the highly conserved phosphotyrosine (pY+0) SH2 binding pocket stattic is not a specific hSTAT3 inhibitor, but is equally effective towards hSTAT1 and hSTAT2. This was confirmed in Human

Micro-vascular Endothelial Cells (HMECs) in vitro, in which static inhibited interferon-alpha-induced phosphorylation of all three STATs. Likewise, fludarabine inhibits both hSTAT1 and hSTAT3 phosphorylation, but not hSTAT2, by competing with the highly conserved pY+0 and pY-X binding sites, which are less well-preserved in hSTAT2. Moreover we observed that in HMECs in vitro fludarabine inhibits cytokine and lipopolysaccharide-induced phosphorylation of hSTAT1 and hSTAT3 but does not affect hSTAT2. Finally, multiple sequence alignment of STAT-SH2 domain sequences confirmed high conservation between hSTAT1 and hSTAT3, but not hSTAT2, with respect to static and fludarabine binding sites. Together our data offer a molecular basis that explains STAT cross-binding specificity of static and fludarabine, thereby questioning the present selection strategies of SH2 domain-based competitive small inhibitors.

[634]

**TÍTULO / TITLE:** - The siRNA cocktail targeting VEGF and HER2 inhibition on the proliferation and induced apoptosis of gastric cancer cell.

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

**REVISTA / JOURNAL:** - Mol Cell Biochem. 2013 Oct 26.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1850-0](#)

**AUTORES / AUTHORS:** - Liu K; Chen H; You Q; Shi H; Wang Z

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiothoracic Surgery, The Affiliated Hospital of Nantong University, 20 Xisi Road, Nantong, 226001, Jiangsu, People's Republic of China.

**RESUMEN / SUMMARY:** - The aim of this study was to investigate the inhibitory effect of a siRNA cocktail targeting Vascular endothelial growth factor (VEGF) and Human epidermal growth factor receptor 2 (HER2) on cell proliferation, induced apoptosis and the expression of VEGF and HER2 in human gastric carcinoma cell. The silencing rate of pre-designed siRNAs that targeted VEGF and HER2 was detected by Real-time Quantitative PCR (RT-QPCR) analysis. Furthermore, the best silencing siRNA that targeted VEGF and HER2 was prepared as a cocktail to co-knockdown VEGF and HER2 expression at both mRNA and protein levels which were detected by RT-QPCR and Western blot analysis. Cell proliferation inhibition rates were determined by CCK8 assay. The effect of siRNA cocktail on cell apoptosis was determined by flow cytometry. The migration inhibition of siRNA cocktail was analyzed by wound-healing assay. The ability of VEGF to induce endothelial cells to proliferate was examined in HUVECs by the method of tube formation assay. The pre-designed siRNAs could inhibit VEGF and HER2 mRNA level. siRNA cocktail, and co-downregulation of VEGF and HER2 result in significant inhibition of gastric cancer growth and migration in vitro. The inhibition of VEGF and HER2 expressions can induce apoptosis of SGC-7901 cells.

[635]

**TÍTULO / TITLE:** - Design, synthesis, and biological evaluation of bone-targeted proteasome inhibitors for multiple myeloma.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Dec 1;23(23):6455-8. doi: 10.1016/j.bmcl.2013.09.043. Epub 2013 Sep 21.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.09.043](https://doi.org/10.1016/j.bmcl.2013.09.043)

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**RESUMEN / SUMMARY:** - Multiple myeloma (MM) is an incurable neoplasm characterized by devastating and progressive bone destruction. Standard chemotherapeutic agents have not been effective at significantly prolonging the survival of MM patients and these agents are typically associated with often severe, dose-limiting side effects. There is great need for methods to target the delivery of novel, effective cytotoxic agents specifically to bone, where myeloma cells reside. We have synthesized and evaluated the effects of the bone-targeted proteasome inhibitors PS-341-BP-1, PS-341-BP-2 and MG-262-BP on cell proliferation using the mouse 5TGM1 and human RPMI 8226 cell lines in vitro. The compounds exhibit strong cytotoxicity on MM cell lines and reduce the number of viable cells in a dose dependent manner.

[636]

**TÍTULO / TITLE:** - Low level of high-density lipoprotein cholesterol correlates with poor prognosis in extranodal natural killer/T cell lymphoma.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Oct 13.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1284-z](https://doi.org/10.1007/s13277-013-1284-z)

**AUTORES / AUTHORS:** - Wang L; Chi PD; Chen H; Xiang J; Xia ZJ; Zhang YJ

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, People's Republic of China.

**RESUMEN / SUMMARY:** - Studies have found that lymphoma patients often exhibit abnormal lipid metabolism, and a decrease in serum high-density lipoprotein cholesterol (HDL-C) may occur during lymphomagenesis and tumor growth. However, no literatures have investigated the role of HDL-C in patients with extranodal natural killer/T cell lymphoma (ENKTL). In this study, we retrospectively reviewed the HDL-C level in 107 patients newly diagnosed with ENKTL that received either L-asparaginase-based regimen or EPOCH regimen as induction chemotherapy, and evaluated its prognostic value. The mean level of HDL-C was 1.10 mmol/L (range, 0.15-2.63), and the HDL-C level was significantly lower in patients with elevated LDH and beta 2-microglobulin (beta2-MG) ( $p = 0.017$  and  $0.001$ , respectively) and those who underwent disease progression and died ( $p = 0.031$  and  $0.007$ , respectively). In univariate survival analysis, higher Eastern Cooperative Oncology Group performance status score ( $\geq 1$ ), Ann Arbor stage III-IV, elevated LDH, higher international prognostic index (IPI) score ( $\geq 2$  vs. 1 vs. 0), decreased HDL-C level ( $< 40$  mg/dL), elevated beta2-MG level, and response status after induction chemotherapy correlated significantly with poor progression-free survival (PFS) and overall survival (OS) ( $p < 0.05$ ). In a multivariate Cox regression model that included IPI score, HDL-C level,

beta2-MG level, and response status after induction chemotherapy, it was found that HDL-C level and response status after chemotherapy were independent prognostic factors for OS ( $p = 0.014$  and  $0.010$ , respectively) and PFS ( $p = 0.016$  and  $0.020$ , respectively). In conclusion, HDL-C was found to be a valuable independent prognostic factor in ENKTL, and the mechanism needs to be further investigated, which may offer the possibility of therapeutic targets.

[637]

**TÍTULO / TITLE:** - Overexpression of stathmin 1 confers an independent prognostic indicator in nasopharyngeal carcinoma.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1345-3](#)

**AUTORES / AUTHORS:** - Hsu HP; Li CF; Lee SW; Wu WR; Chen TJ; Chang KY; Liang SS; Tsai CJ; Shiue YL

**INSTITUCIÓN / INSTITUTION:** - Center of Medical Education, Chi-Mei Medical Center, Tainan, Taiwan.

**RESUMEN / SUMMARY:** - Data mining on public domain identified that stathmin 1 (STMN1) transcript was significantly higher expressed in nasopharyngeal carcinoma (NPC). Also known as the oncoprotein 18, STMN1 performs an important function in regulating rapid microtubule remodeling of the cytoskeleton in response to the cellular conditions. Immunoprecipitation of STMN1 was retrospectively assessed in biopsies of 124 consecutive NPC patients without initial distant metastasis and treated with consistent guidelines. The outcome was correlated with clinicopathological features and patient survivals. Results indicated that high STMN1 expressions (50 %) were correlated with advanced age ( $p = 0.027$ ), higher T stage ( $p = 0.003$ ), and overall clinical stage ( $p = 0.006$ ) by the 7<sup>th</sup> American Joint Committee of Cancer Staging. In multivariate analyses, high STMN1 expression emerged as an independent prognosticator for worse disease-specific survival ( $p = 0.001$ ), distal metastasis-free survival ( $p = 0.003$ ), and local recurrence-free survival ( $p = 0.006$ ). Exogenous expression of E2F transcription factor 1 (E2F1) or/and its dimeric partner, transcription factor Dp-1 (TFDP1), notably induced the STMN1 protein level in a NPC-derived cell line, TW01. Accordingly, high STMN1 protein level is commonly associated with adverse prognosticators and confers tumor aggressiveness in patients with NPC, and its upregulation might be attributed to E2F1 and/or TFDP1 transactivation.

[638]

**TÍTULO / TITLE:** - Apoptotic markers in a prostate cancer cell line: effect of ellagic acid.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2804-10. doi: 10.3892/or.2013.2757. Epub 2013 Sep 30.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2757](#)

**AUTORES / AUTHORS:** - Vanella L; Di Giacomo C; Acquaviva R; Barbagallo I; Cardile V; Kim DH; Abraham NG; Sorrenti V

**INSTITUCIÓN / INSTITUTION:** - Department of Drug Science, Section of Biochemistry, University of Catania, I-95125 Catania, Italy.

**RESUMEN / SUMMARY:** - Ellagic acid (EA) inhibits cell growth and induces apoptosis in cultured cells; however, the precise molecular mechanism involved in EA-induced apoptosis in prostate cancer cells is unknown. The aim of the present study was to delineate possible apoptotic pathway(s) involved in the EA-mediated chemotherapeutic effects in the LNCaP human prostatic cancer cell line. EA produced anti-proliferative effects through inhibition of rapamycin (mTOR) activation and a reduction in intracellular levels of beta-catenin. Moreover, we demonstrated that EA induced apoptosis via downregulation of the anti-apoptotic proteins, silent information regulator 1 (SIRT1), human antigen R (HuR) and heme oxygenase-1 (HO-1). EA modulated the expression of apoptosis-inducing factor (AIF) resulting in a significant increase in reactive oxygen species (ROS) levels and the activation of caspase-3. Finally, we demonstrated that EA reduced both transforming growth factor-beta (TGF-beta) and interleukin-6 (IL-6) levels. EA treatment resulted in the increased expression of the tumor suppressor protein p21 and increased the percentage of apoptotic cells. In conclusion, the results suggest that EA treatment represents a new and highly effective strategy in reducing prostate cancer carcinogenesis.

[639]

**TÍTULO / TITLE:** - Targeting Tamoxifen to Breast Cancer Xenograft Tumours: Preclinical Efficacy of Folate-Attached Nanoparticles Based on Alginate-Cysteine/Disulphide-Bond-Reduced Albumin.

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

**REVISTA / JOURNAL:** - Pharm Res. 2013 Nov 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11095-013-1247-5](#)

**AUTORES / AUTHORS:** - Martinez A; Muniz E; Teijon C; Iglesias I; Teijon JM; Blanco MD

**INSTITUCIÓN / INSTITUTION:** - Departamento de Farmacología, Facultad de Farmacia Universidad Complutense de Madrid, Madrid, España.

**RESUMEN / SUMMARY:** - **PURPOSE:** In vivo evaluation of tamoxifen (TMX)-loaded folate-targeted nanoparticles prepared from a mixture of disulphide bond reduced bovine serum albumin (BSA-SH) and alginate-cysteine (ALG-CYS) as targeted delivery systems of TMX to tumour tissues. **METHODS:** TMX in solution, TMX included into folate-nanoparticles and their non-targeted analogues were intravenously administered to nude mice carrying xenograft MCF-7 tumours. The antitumor activity of these systems was characterized in terms of tumour growth rate, histological and immunohistochemical analysis of tumour tissues and TMX biodistribution. **RESULTS:** TMX-folate-attached nanoparticles caused tumour remission whereas free TMX or TMX-non-targeted nanoparticles could only stop the tumour development. The histological evaluation of tumour tissues showed that those treated with folate-conjugated systems presented the most quiescent and disorganized structures. Additionally, the lowest concentrations of TMX accumulated in non-targeted organs were also found after administration of the drug using this formulation. **CONCLUSIONS:** This study demonstrated that TMX-loaded folate-targeted systems were capable of reaching tumour sites, so enhancing the in vivo anticancer action of TMX, and allowing a new administration route to be applied and some of the current TMX therapy problems to be overcome.

[640]

**TÍTULO / TITLE:** - Angiogenesis in Canine Mammary Tumours: A Morphometric and Prognostic Study.

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

**REVISTA / JOURNAL:** - J Comp Pathol. 2013 Nov 11. pii: S0021-9975(13)00159-X. doi: 10.1016/j.jcpa.2013.09.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.jcpa.2013.09.005](#)

**AUTORES / AUTHORS:** - Sleeckx N; Van Brantegem L; Van den Eynden G; Fransen E; Casteleyn C; Van Cruchten S; Veldhuis Kroeze E; Van Ginneken C

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**RESUMEN / SUMMARY:** - Angiogenesis in canine mammary tumours (CMTs) has been described previously; however, only the intratumoural (IT) region has been studied and information on peritumoural (PT) angiogenesis is lacking. In this study, the blood vessel density (BVD), blood vessel perimeter (BVP) and blood vessel area (BVA) in IT and PT regions of 56 benign CMTs, 55 malignant CMTs and 13 samples of normal mammary gland tissue were analyzed. In addition, the blood endothelial cell proliferation (BCEP) as an indicator of ongoing angiogenesis was investigated. The prognostic value of each parameter was also examined. Blood vessels and proliferating blood endothelial cells were present in IT and PT regions of both benign and malignant tumours. The vessels in the PT region had a significantly higher area and perimeter compared with those in the IT region. Malignant tumours showed significantly more vessels with a smaller total BVA and a higher BCEP compared with benign tumours and control tissue. In the PT regions there was a significantly higher BVD, BVA and BVP compared with the vessels in control tissue. Only the IT and PT BVD and PT BCEP in benign tumours allowed prediction of survival. The morphology of blood vessels in CMTs shows similarities with those in human breast cancer, which strengthens the case for the use of dogs with CMTs in comparative oncology trials.

[641]

**TÍTULO / TITLE:** - Meta-Analysis of the Prognostic and Diagnostic Significance of Serum/Plasma Osteopontin in Hepatocellular Carcinoma.

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

**REVISTA / JOURNAL:** - J Clin Gastroenterol. 2013 Nov 15.

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

[1097/MCG.0000000000000018](#)

**AUTORES / AUTHORS:** - Cheng J; Wang W; Sun C; Li M; Wang B; Lv Y

**INSTITUCIÓN / INSTITUTION:** - \*Department of Hepatobiliary Surgery, First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University daggerDepartment of Hospital Quality Management, 451 Hospital of the PLA, Shaanxi, People's Republic of China.

**RESUMEN / SUMMARY:** - GOALS:: The aim of this study was to perform a meta-analysis to evaluate the prognostic and diagnostic significance of serum/plasma osteopontin (OPN) in hepatocellular carcinoma (HCC). BACKGROUND:: The prognostic and diagnostic value of serum/plasma OPN in HCC remain controversial. STUDY:: Eligible studies were identified through a systematic literature search. A meta-

analysis of 8 studies (4 for prognosis and 4 for diagnosis, 1399 patients) was performed to estimate the association between serum/plasma-based OPN elevation and overall survival (OS) and disease-free survival (DFS) in HCC patients, and to evaluate the accuracy of plasma OPN and alpha-fetoprotein (AFP) in the diagnosis of HCC. Subgroup analyses were also performed in the meta-analysis. RESULTS:: We found that serum/plasma-based OPN elevation was significantly associated with poor OS (HR, 1.96; 95% CI, 1.47-2.61; P<0.00001) and DFS (HR, 1.80; 95% CI, 1.43-2.26; P<0.00001) in HCC. The summary estimates for plasma OPN and AFP in diagnosing HCC in the studies included were as follows: sensitivity, 88% (95% CI, 84%-91%) versus 68% (95% CI, 63%-73%); specificity, 87% (95% CI, 83%-90%) versus 97% (95% CI, 94%-99%); diagnostic odds ratio, 62.87 (95% CI, 10.90-362.60) versus 49.09 (95% CI, 11.36-212.10); and area under SROS, 0.91 (95% CI, 0.85-0.97) versus 0.68 (95% CI, 0.45-1.03). CONCLUSIONS:: The current evidence indicates that serum/plasma-based OPN seems to have significant predictive ability for estimating survival in HCC, and plasma OPN has a comparable accuracy to AFP for the diagnosis of HCC, although the diagnostic value of plasma OPN for early or AFP-negative HCC remains to be assessed by further studies.

[642]

**TÍTULO / TITLE:** - Decorin-mediated inhibition of cholangiocarcinoma cell growth and migration and promotion of apoptosis are associated with E-cadherin in vitro.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 24.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1402-y](#)

**AUTORES / AUTHORS:** - Yu X; Zou Y; Li Q; Mao Y; Zhu H; Huang G; Ji G; Luo X; Yu C; Zhang X

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, The Second Affiliated Hospital of Nanjing Medical University, 121 Jiangjiayuan, Xiaguan District, Nanjing, 210000, China, [yuxiang861120@163.com](mailto:yuxiang861120@163.com).

**RESUMEN / SUMMARY:** - Emerging evidences have shown that decorin expression is significantly reduced in many cancer tissues and cancer cells. However, its biological role and clinical significance in cholangiocarcinoma development and progression are unknown. In this study, immunohistochemistry was conducted to investigate the expression of decorin in cholangiocarcinomas. The results showed that decorin levels markedly decreased in 44 cholangiocarcinoma tissues compared to 40 adjacent normal tissues. The analysis between decorin expression and clinicopathological characteristics in cholangiocarcinoma patients showed that patients with low levels of decorin expression had a relatively poor prognosis. Moreover, recombinant human decorin treatment and overexpression of decorin in cholangiocarcinoma cells could inhibit cell proliferation, migration, and invasion and promote apoptosis. Furthermore, the E-cadherin expression significantly increased after decorin overexpression or use of recombinant human decorin in cholangiocarcinoma cells. Our findings indicated that downregulation of decorin may be identified as a poor prognostic biomarker in cholangiocarcinomas. Also, decorin-mediated inhibition of cholangiocarcinoma cell growth, migration, and invasion and promotion of cell apoptosis might be through regulation of the expression of E-cadherin in vitro.

[643]

**TÍTULO / TITLE:** - Prediction and validation of apoptosis through cytochrome P450 activation by benzo[a]pyrene.

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

**REVISTA / JOURNAL:** - Chem Biol Interact. 2013 Nov 15. pii: S0009-2797(13)00281-0. doi: 10.1016/j.cbi.2013.11.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.cbi.2013.11.005](#)

**AUTORES / AUTHORS:** - Das DN; Panda PK; Mukhopadhyay S; Sinha N; Mallick B; Behera B; Maiti TK; Bhutia SK

**INSTITUCIÓN / INSTITUTION:** - Department of Life Sciences, National Institute of Technology, Rourkela, India.

**RESUMEN / SUMMARY:** - Polycyclic aromatic hydrocarbons (PAHs) processed by cytochrome P450 (CYP450) during metabolism is well reported to induce carcinogenesis. The present study has developed a new approach to examine apoptotic activity of a known PAH called benzo[a]pyrene (B[a]P), using protein-ligand and protein-protein interaction through in silico approach, followed by in vitro validation. In silico study showed that the conformational changes and energies involved in the binding of B[a]P to CYP1B1 was crucial with its target proteins. The data showed that activated B[a]P had high affinity to bind with aryl hydrocarbon receptor (AhR) with binding energy of -601.97kcal/mol. Interestingly, B[a]P-CYP1B1 complex showed strong binding affinity for caspase-8, -9, -3 with binding energy of -625.5, -479.3 and -514.2kcal/mol respectively. Moreover, the docking of specific caspase inhibitors in the complex showed weak interaction with low binding energy value as compared to B[a]P-CYP1B1 caspase complexes. To validate our in silico work, we showed B[a]P treated HaCaT cells triggered apoptosis with increase in caspase 8, caspase 9 and caspase 3/7 level. Further, in vitro work confirmed that B[a]P induced apoptosis was significantly suppressed in Ac-DEVD-CMK pre-treated cells. In addition, knockdown of CYP1B1 suppressed B[a]P induced apoptosis in HaCaT cells confirming a pivotal role of CYP1B1 in B[a]P induced apoptosis. Interestingly, through in silico modeling, we screened clotrimazole as a potent CYP1B1 inhibitor which completely inhibited B[a]P mediated activation. This hypothesis was validated by MTT assay, caspase activation measurement and showed remarkable inhibition of B[a]P induced cell death; thereby, highlighting a potent therapeutic role for industrial pollution associated diseases.

[644]

**TÍTULO / TITLE:** - Effect of Ursolic Acid on MAPK in Cyclin D1 Signaling and RING-Type E3 Ligase (SCF E3s) in Two Endometrial Cancer Cell Lines.

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

**REVISTA / JOURNAL:** - Nutr Cancer. 2013 Oct;65(7):1026-33. doi: 10.1080/01635581.2013.810292. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.810292](#)

**AUTORES / AUTHORS:** - Achiwa Y; Hasegawa K; Udagawa Y

**INSTITUCIÓN / INSTITUTION:** - a Faculty of Obstetrics and Gynecology, School of Medicine, Fujita Health University, Toyoake, Aichi, Japan.

**RESUMEN / SUMMARY:** - Cyclin D1 regulates G1 progression and is important in the development and proliferation of various human cancers. Cyclin D1 gene expression is

activated by the Ras kinase cascade. Nuclear cyclin D1 levels are dependent on cytoplasmic degradation of cyclin D1 via ubiquitin-mediated proteolysis. We sought to determine whether the important MAPK signaling pathway, in the cyclin D1 cascade, including FBXW8, Cullin1, and the ubiquitination pathway mediated these effects. Ursolic acid (UA) treatment of SNG-2 cells, an endometrial cancer cell line, decreased cyclin D1, pERK1/2, FBXW8, and Cullin1 levels in a dose- and time-dependent manner. RING-type E3 ligase consists of Cullin1, Rbx, Skp1, and a member of the F-box protein family. In SNG-2, both dose- and time-dependent inhibition of Rbx 1 were observed following treatment with UA. Moreover, in HEC108 cells, another endometrial cancer cell line, UA treatment decreased cyclin D1, pERK1/2, and Cullin1 levels in a dose- and time-dependent manner and UA markedly inhibited FBXW8. Treatment of HEC108 cells moderately decreased Rbx1 in a dose- and time-dependent fashion. In contrast, UA treatment increased ubiquitinated proteins in a dose- and time-dependent manner in both cell lines. RING-type E3 ligase accumulated in the cytoplasm following UA treatment of SNG-2 cells. That in turn prevented cytoplasmic degradation of cyclin D1 via RING-type E3 (SCF E3s) ligase. In conclusion, our study found inhibition of the MAPK- cyclin D1 pathway and RING type E3 ligase (SCF E3s) in both endometrial cancer cell lines. Furthermore, CD36 was noted as a cell surface receptor for UA.

[645]

**TÍTULO / TITLE:** - Serum response factor induces epithelial to mesenchymal transition with resistance to sorafenib in hepatocellular carcinoma.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2014 Jan;44(1):129-36. doi: 10.3892/ijo.2013.2154. Epub 2013 Oct 30.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.2154](#)

**AUTORES / AUTHORS:** - Bae JS; Noh SJ; Kim KM; Jang KY; Chung MJ; Kim DG; Moon WS

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Chonbuk National University, Medical School, Research Institute of Clinical Medicine of Chonbuk National University Hospital and Research Institute for Endocrine Sciences, Jeonju 561-756, Republic of Korea.

**RESUMEN / SUMMARY:** - The epithelial to mesenchymal transition (EMT) is a crucial process in tumor progression. EMT of tumor cells not only causes increased metastasis, but also contributes to drug resistance. Serum response factor (SRF) is a transcription factor that plays a central role in carcinogenesis and tumor progression in several types of cancers. We investigated the effect of EMT-related SRF, focusing on its promotion of chemoresistance against sorafenib in hepatocellular carcinoma (HCC). We examined SRF and Snail expression in 146 cases of HCCs by immunohistochemistry. We also examined the chemoresistance effect of SRF in HCC cells by transfecting HLE cells with SRF cDNA and SH-J1 cells with SRF antisense cDNA. Expression of SRF and Snail were detected in 37.6% (55 of 146 cases) and in 12.3% (18 of 146 cases) of the HCCs, respectively. None of the tumor-free liver tissues showed SRF or Snail expression. SRF expression was closely correlated with the expression of Snail ( $p < 0.001$ ) and expression of both SRF and Snail showed significant correlation with the high histological grade ( $p = 0.015$  and  $0.003$ , respectively). Overexpression of SRF in HLE cells led to increased expression of mesenchymal

markers, as well as increased cell growth and colony formation. Overexpression of SRF also led to a significant reduction in the cytotoxic effect of sorafenib in HLE cells. Conversely, inhibition of SRF expression in the SH-J1 cells significantly enhanced the apoptotic effects of sorafenib, along with the reduced expression of mesenchymal markers and restored the expression of E-cadherin. These results suggest that SRF is critical for HCC to acquire a mesenchymal phenotype, which leads to resistance against a sorafenib-mediated apoptotic effect.

[646]

**TÍTULO / TITLE:** - Enhanced cytotoxicity of optimized liposomal genistein via specific induction of apoptosis in breast, ovarian and prostate carcinomas.

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

**REVISTA / JOURNAL:** - J Drug Target. 2013 Dec;21(10):1001-11. doi: 10.3109/1061186X.2013.847099. Epub 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [3109/1061186X.2013.847099](#)

**AUTORES / AUTHORS:** - Phan V; Walters J; Brownlow B; Elbayoumi T

**INSTITUCIÓN / INSTITUTION:** - Arizona College of Osteopathic Medicine, Midwestern University, Glendale, AZ, USA and.

**RESUMEN / SUMMARY:** - Abstract Clinical use of genistein against cancer is limited by its extremely low aqueous solubility, poor bioavailability and pharmacokinetics. Based on structural analogy with steroidal compounds, liposomal vehicle compositions were designed and optimized for maximum incorporation of genistein's flavonoid structure. Model conventional and stealth liposomes of genistein (GenLip) - incorporating unsaturated phospholipids and cholesterol - have demonstrated enhanced drug solubilization (over 350-folds > aqueous drug solution), shelf-life stability, and extended release profile. Owing to effective cellular delivery, preservation of genistein's antioxidant activity was confirmed through marked neutralization of peroxides via GenLip, in both quantitative and microscopic fluorescent-probe oxidation assays. Furthermore, significant broad-spectrum anticancer efficacy of GenLip, in murine and human cancer cell lines ( $p < 0.05-0.001$ ), was achieved in a concentration and time-dependent manner - approx. 5-7 lower IC50 values versus all non-incorporated drug controls. Indicative of key pro-apoptotic activity, GenLip produced DNA laddering, with 1/3 of free drug solution content, and resulted in the highest induction level of P53-independent apoptotic pathway markers, compared to all treatments, in our assays (namely, mitochondrial polarization, and caspase-3/7 enzymes). Our proof-of-principle pharmaceutical design of genistein-loaded liposomes shows optimal loading capacity and physico-chemical properties, which improved cellular delivery and specific pro-apoptotic effectiveness of incorporated drug, against various cancers.

[647]

**TÍTULO / TITLE:** - A bismuth diethyldithiocarbamate compound promotes apoptosis in HepG2 carcinoma, cell cycle arrest and inhibits cell invasion through modulation of the NF-kappaB activation pathway.

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

**REVISTA / JOURNAL:** - J Inorg Biochem. 2014 Jan;130:38-51. doi: 10.1016/j.jinorgbio.2013.09.018. Epub 2013 Oct 10.

●● Enlace al texto completo (gratis o de pago) [1016/j.jinorgbio.2013.09.018](https://doi.org/10.1016/j.jinorgbio.2013.09.018)

**AUTORES / AUTHORS:** - Ishak DH; Ooi KK; Ang KP; Akim AM; Cheah YK; Nordin N; Halim SN; Seng HL; Tiekink ER

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia.

**RESUMEN / SUMMARY:** - The compound with R=CH<sub>2</sub>CH<sub>3</sub> in Bi(S<sub>2</sub>CNR<sub>2</sub>)<sub>3</sub> (1) is highly cytotoxic against a range of human carcinoma, whereas that with R=CH<sub>2</sub>CH<sub>2</sub>OH (2) is considerably less so. Both 1 and 2 induce apoptosis in HepG2 cells with some evidence for necrosis induced by 2. Based on DNA fragmentation, caspase activities and human apoptosis PCR-array analysis, both the extrinsic and intrinsic pathways of apoptosis have been shown to occur. While both compounds activate mitochondrial and FAS apoptotic pathways, compound 1 was also found to induce another death receptor-dependent pathway by induction of CD40, CD40L and TNF-R1 (p55). Further, 1 highly expressed DAPK1, a tumour suppressor, with concomitant down-regulation of XIAP and NF-kappaB. Cell cycle arrest at the S and G2/M phases correlates with the inhibition of the growth of HepG2 cells. The cell invasion rate of 2 is 10-fold higher than that of 1, a finding correlated with the down-regulation of survivin and XIAP expression by 1. Compounds 1 and 2 interact with DNA through different binding motifs with 1 interacting with AT- or TA-specific sites followed by inhibition of restriction enzyme digestion; 2 did not interfere with any of the studied restriction enzymes.

[648]

**TÍTULO / TITLE:** - Overexpression of Glucose Transporter-1 (GLUT-1) Predicts Poor Prognosis in Epithelial Ovarian Cancer.

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

**REVISTA / JOURNAL:** - Cancer Invest. 2013 Nov;31(9):607-15. doi: 10.3109/07357907.2013.849722.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.849722](https://doi.org/10.3109/07357907.2013.849722)

**AUTORES / AUTHORS:** - Cho H; Lee YS; Kim J; Chung JY; Kim JH

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea,1.

**RESUMEN / SUMMARY:** - Illumina microarray was used to identify differentially expressed genes in three epithelial ovarian cancer (EOC) cells. To validate the microarray data, mRNA and protein level of glucose transporter-1 (GLUT-1) was examined. GLUT-1 had an EOC/normal cells ratio of 5.51 based on microarray. Real-time PCR and immunohistochemistry demonstrated that GLUT-1 expression was significantly increased in EOC (p = .029 and p < .001, respectively). On survival analysis, GLUT-1 overexpression (HR = 4.80, p = .027) and lymph node metastases (HR = 8.35, p = .016) conferred a significantly worse overall survival. In conclusion, GLUT-1 expression is remarkably upregulated in EOC and predicts a poor overall survival.

[649]

**TÍTULO / TITLE:** - Clearance of BRAF inhibitor-associated keratoacanthomas by systemic retinoids.

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

**REVISTA / JOURNAL:** - Br J Dermatol. 2013 Oct 11. doi: 10.1111/bjd.12659.

●● Enlace al texto completo (gratis o de pago) [1111/bjd.12659](http://1111/bjd.12659)

**AUTORES / AUTHORS:** - Sachse MM; Wagner G

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, Phlebology and Allergology, Hospital Bremerhaven-Reinkenheide, Germany.

**RESUMEN / SUMMARY:** - vemurafenib is a competitive inhibitor of RAF kinases for treatment of metastatic malignant melanoma. Cutaneous adverse effects mainly comprise of benign lesions such as hair follicle changes (e.g. alopecia), rash, photosensitivity, verrucal keratosis, palmar-plantar hyperkeratosis, and keratosis pilaris-like eruptions. Of note, up to one third of patients treated with vemurafenib develop keratoacanthomas (KAs) and/or cutaneous squamous-cell carcinomas.<sup>1,2,3</sup> Surgery remains the main treatment of choice in RAF induced KAs. In this brief report, we present the clearance of 19 KAs by systemic retinoids in a patient with metastatic malignant melanoma. 14 months after initiation of vemurafenib treatment, there is no evidence of visceral metastasis or recurrence of KA. This article is protected by copyright. All rights reserved.

[650]

**TÍTULO / TITLE:** - Distinct poor prognostic subgroups of acute myeloid leukaemia, FLT3-ITD and P-glycoprotein-positive, have contrasting levels of FOXO1.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Nov 8. pii: S0145-2126(13)00388-3. doi: 10.1016/j.leukres.2013.10.030.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.10.030](http://1016/j.leukres.2013.10.030)

**AUTORES / AUTHORS:** - Seedhouse CH; Mills KI; Ahluwalia S; Grundy M; Shang S; Burnett AK; Russell NH; Pallis M

**INSTITUCIÓN / INSTITUTION:** - Department of Haematology, University of Nottingham, Nottingham, UK. Electronic address: [claire.seedhouse@nottingham.ac.uk](mailto:claire.seedhouse@nottingham.ac.uk).

**RESUMEN / SUMMARY:** - Regulation of ABCB1 (P-glycoprotein/Pgp) in AML was investigated. In a historical cohort with Pgp and transcriptional regulator expression profiling data available (n=141), FOXO1 correlated with Pgp protein expression. This was confirmed in an independent cohort (n=204). Down-regulation (siRNA) or hyperactivation (nicotinamide) of FOXO1 led to corresponding changes in Pgp. Low FOXO1 expression correlated with FLT3-ITDs (p<0.001) and siRNA inhibition of FLT3-ITD up-regulated FOXO1. As FOXO1 is a key growth regulator, it may underpin biological differences between Pgp-positive clones (low WBC and primary resistant disease) and clones with a FLT3-ITD (associated with a high WBC and early relapse).

[651]

**TÍTULO / TITLE:** - Sesamin Induces cell cycle arrest and apoptosis through the inhibition of signal transducer and activator of transcription 3 signalling in human hepatocellular carcinoma cell line HepG2.

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

**REVISTA / JOURNAL:** - Biol Pharm Bull. 2013;36(10):1540-8.

**AUTORES / AUTHORS:** - Deng P; Wang C; Chen L; Wang C; Du Y; Yan X; Chen M; Yang G; He G

**INSTITUCIÓN / INSTITUTION:** - The Genetic Engineering International Cooperation Base of Chinese Ministry of Science and Technology, Key Laboratory of Molecular Biophysics of Chinese Ministry of Education, College of Life Science and Technology, Huazhong University of Science & Technology (HUST).

**RESUMEN / SUMMARY:** - Sesamin, one of the most abundant lignans in sesame seeds, has been shown to exhibit various pharmacological effects. The aim of this study was to elucidate whether sesamin promotes cell cycle arrest and induces apoptosis in HepG2 cells and further to explore the underlying molecular mechanisms. Here, we found that sesamin inhibited HepG2 cell growth by inducing G2/M phase arrest and apoptosis. Furthermore, sesamin suppressed the constitutive and interleukin (IL)-6-induced signal transducer and activator of transcription 3 (STAT3) signalling pathway in HepG2 cells, leading to regulate the downstream genes, including p53, p21, cyclin proteins and the Bcl-2 protein family. Our studies showed that STAT3 signalling played a key role in sesamin-induced G2/M phase arrest and apoptosis in HepG2 cells. These findings provided a molecular basis for understanding of the effects of sesamin in hepatocellular carcinoma tumour cell proliferation. Therefore, sesamin may thus be a potential chemotherapy drug for liver cancer.

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[652]

**TÍTULO / TITLE:** - Hsa-miR-132 Regulates Apoptosis in Non-Small Cell Lung Cancer Independent of Acetylcholinesterase.

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

**REVISTA / JOURNAL:** - J Mol Neurosci. 2013 Oct 26.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12031-013-0136-z](#)

**AUTORES / AUTHORS:** - Zhang B; Lu L; Zhang X; Ye W; Wu J; Xi Q; Zhang X

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, 200031, China.

**RESUMEN / SUMMARY:** - MiR-132 is enriched in the central nerve system and is thought to be involved in neuronal development, maturation and function, and to be associated with several neurological disorders including Alzheimer's disease. In addition to its documented neuronal functions, an emerging role for miR-132 in tumorigenesis has been suggested. Recently, hsa-miR-132 was shown to be modulated in different tumor types. However, its role in non-small cell lung cancer (NSCLC) remains unclear. Here, we show that hsa-miR-132 can initiate apoptosis in NSCLC cells to dramatically attenuate tumor formation in nude mice independent of its effect on the proliferation/apoptosis-associated gene, acetylcholinesterase (AChE). Interestingly, hsa-miR-132 has no pro-apoptotic effect in normal pulmonary trachea epithelium. Taken together, these results suggest that hsa-miR-132 represses NSCLC growth by inducing apoptosis independent of AChE.

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[653]

**TÍTULO / TITLE:** - Characterizing the Role of PCDH9 in the Regulation of Glioma Cell Apoptosis and Invasion.

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

**REVISTA / JOURNAL:** - J Mol Neurosci. 2013 Nov 9.

●● Enlace al texto completo (gratis o de pago) [1007/s12031-013-0133-2](https://doi.org/10.1007/s12031-013-0133-2)

**AUTORES / AUTHORS:** - Wang C; Tao B; Li S; Li B; Wang X; Hu G; Li W; Yu Y; Lu Y; Liu J

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, The 105<sup>th</sup> Hospital of PLA, 424 West Changjiang Road, Hefei, Anhui, 230000, China.

**RESUMEN / SUMMARY:** - PCDH9, a member of the protocadherin superfamily, is frequently lost in many different cancer types. This study aimed to detect PCDH9 expression in glioma tissues. This study also assessed the effects of PCDH9 expression in two different glioma cell lines. This was accomplished by manipulating PCDH9 expression in these glioma cell lines. The data showed that the expression of PCDH9 mRNA and protein was significantly decreased in gliomas compared to normal brain tissues. Lentivirus carrying PCDH9 cDNA restored PCDH9 expression in the U87 and U251 glioma cell lines. PCDH9 restoration in these cell lines reduced tumor cell viability, induced apoptosis, and caused G0/G1 cell cycle arrest. PCDH9 expression also suppressed the colony formation ability and invasion capacity of U87 and U251 cells. Molecularly, the restoration of PCDH9 expression upregulated Bax protein expression, but downregulated Bcl-2 and cyclin D1 expression. These data from the current study suggest that the loss of PCDH9 expression could contribute to glioma development and/or progression. Further studies will evaluate PCDH9 expression as a biomarker for the early detection of gliomas and as a prognostic indicator for this cancer type.

[654]

**TÍTULO / TITLE:** - New orally active proteasome inhibitors in multiple myeloma.

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

**REVISTA / JOURNAL:** - Leuk Res. 2013 Oct 29. pii: S0145-2126(13)00372-X. doi: 10.1016/j.leukres.2013.10.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.10.018](https://doi.org/10.1016/j.leukres.2013.10.018)

**AUTORES / AUTHORS:** - Allegra A; Alonci A; Gerace D; Russo S; Innao V; Calabro L; Musolino C

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology University of Messina, Messina, Italy. Electronic address: [alessandro.allegra@tin.it](mailto:alessandro.allegra@tin.it).

**RESUMEN / SUMMARY:** - Bortezomib is the first proteasome inhibitor approved for the therapy of multiple myeloma (MM). Although Bortezomib has renovated the treatment of MM, a considerable proportion of subjects fail to respond to Bortezomib treatment and almost all patients relapse from this drug either alone or when used in combination therapies. However, the good clinical outcome of Bortezomib treatment in MM patients gave impulsion for the development of second generation proteasome inhibitors with the ambition of improving efficacy of proteasome inhibition, enhancing antitumor activity, and decreasing toxicity, as well as providing flexible dosing schedules and patient convenience. This review provides an overview of the role of oral proteasome inhibitors including Marizomib, Oprozomib, Delanzomib, chemical proteasome inhibitors, and cinnabaramides, in the therapy of MM, focusing on developments over the past five years. These emerging drugs with different mechanisms of action have exhibited promising antitumor activity in patients with relapsed/refractory MM, and they are creating chances to target multiple pathways, overcome resistance, and improve clinical outcomes, mainly for those subjects who are refractory to approved agents.

Future steps in the clinical development of oral inhibitors include the optimization of the schedule and the definition of their antitumor activity in MM.

[655]

**TÍTULO / TITLE:** - Lentivirus-mediated shRNA targeting of cyclin D1 enhances the chemosensitivity of human gastric cancer to 5-fluorouracil.

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

**REVISTA / JOURNAL:** - Int J Oncol. 2013 Dec;43(6):2007-14. doi: 10.3892/ijo.2013.2119. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2119](#)

**AUTORES / AUTHORS:** - Seo JH; Jeong ES; Lee KS; Heo SH; Jeong DG; Choi YK

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Animal Medicine, College of Veterinary Medicine, Konkuk University, Seoul 143-701, Republic of Korea.

**RESUMEN / SUMMARY:** - Gastric cancer is one of the major public health problems. Despite new chemotherapeutic treatments, the prognosis of gastric cancer remains poor. 5-Fluorouracil (5-FU) is used as a standard chemotherapy drug in gastric cancer. However, 5-FU resistance develops frequently and is a main cause of chemotherapy failure in human gastric cancer. Overexpression of cyclin D1 is related to rapid cell growth, a poor prognosis and increased chemoresistance in several types of cancers. In this study, we investigated whether treatment of gastric cancer cells with shRNA targeting cyclin D1 (ShCCND1) or 5-FU, alone or in combination, influences the activation of phosphorylated AKT (pAKT) and pNFkappaB, which are markers that are increased in 5-FU chemoresistance. We also investigated the effect of combined treatment with ShCCND1 and 5-FU on cell growth and chemosensitivity to 5-FU in the gastric cancer cell line AGS. The data showed that ShCCND1-mediated cyclin D1 downregulation in AGS cells significantly inhibited cell proliferation, cell mobility and clonogenicity. In addition, combined treatment with ShCCND1 and 5-FU significantly decreased the survival rate of AGS cells, compared to single-treatment with either agent. These results demonstrated that ShCCND1 increases 5-FU chemosensitivity, a conclusion that is also supported by the concomitant reduction in expression of pAKT and pNFkappaB, increase of G1 arrest and induction of apoptosis. Taken together, these data provide further evidence that therapeutic strategies targeting cyclin D1 may have the dual advantage of suppressing the growth of cancer cells, while enhancing their chemosensitivity.

[656]

**TÍTULO / TITLE:** - Salen and tetrahydrosalen derivatives act as effective inhibitors of the tumor-associated carbonic anhydrase XII-A new scaffold for designing isoform-selective inhibitors.

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

**REVISTA / JOURNAL:** - Bioorg Med Chem Lett. 2013 Dec 15;23(24):6759-63. doi: 10.1016/j.bmcl.2013.10.026. Epub 2013 Oct 26.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.10.026](#)

**AUTORES / AUTHORS:** - Carradori S; De Monte C; D'Ascenzio M; Secci D; Celik G; Ceruso M; Vullo D; Scozzafava A; Supuran CT

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza University of Rome, P.le A. Moro 5, 00185 Rome, Italy. Electronic address: [simone.carradori@uniroma1.it](mailto:simone.carradori@uniroma1.it).

**RESUMEN / SUMMARY:** - Salen and tetrahydrosalen derivatives possess metal-chelating properties and have been used as ligands in organic synthesis and as scaffolds for developing therapeutic agents. Fourteen such compounds were synthesized in order to explore their ability to inhibit the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). Human (h) isoforms hCA I, hCA II, hCA IX and hCA XII were included in the investigation. Several aliphatic and aromatic spacers were introduced between the two chelating groups from salen/tetrahydrosalen in order to explore a diverse chemical space for designing CA inhibitors, which incorporate both phenol and polyamine fragments in their molecule. Some of these compounds showed CA inhibitory activity in the low micromolar-nanomolar range and a pronounced selectivity for inhibiting an isoform over-expressed in hypoxic tumors, hCA XII, over hCA I, II and IX.

[657]

**TÍTULO / TITLE:** - HZ08 reverse the aneuploidy-induced cisplatin-resistance in Gastric cancer by modulating the p53 pathway.

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

**REVISTA / JOURNAL:** - Eur J Pharmacol. 2013 Nov 15;720(1-3):84-97. doi: 10.1016/j.ejphar.2013.10.045. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejphar.2013.10.045](#)

**AUTORES / AUTHORS:** - Tang X; Hu G; Xu C; Ouyang K; Fang W; Huang W; Zhang J; Li F; Wang K; Qin X; Li Y

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China; Shanghai ChemPartner Co., Ltd., No. 6 Building, 998 Halei Road, Zhangjiang Hi-Tech Park Pudong New Area, Shanghai 201203, China.

**RESUMEN / SUMMARY:** - We evaluated the influence of DNA aneuploidy on chemotherapy-resistance in human Gastric cancer cell MKN45; we also evaluated the reversal effects of HZ08 on these cells and then preliminary investigated the possible involved pathway. We made use of a pair of human Gastric cancer cell dip-MKN45 (diploid MKN45) and aneu-MKN45 (aneuploid MKN45). Growth inhibition in response to chemotherapeutic drugs was evaluated by CellTiter-Glo Luminescent Cell Viability assay and clone formation assay. Flow cytometry and immuno-assay were applied to evaluate apoptosis and the expression of relative signaling molecules. MKN45 xenograft was generated to evaluate in vivo action. Aneu-MKN45 developed a resistance to cisplatin which could be reversed by HZ08; Flow cytometry and western-blot indicates that HZ08-combination could induce apoptosis and increase the expression of apoptosis-related biomarkers on aneu-MKN45; in vivo study also reflect the same correlation between aneuploidy and cisplatin-resistance, which could be antagonized by HZ08 combination; When investigating the involved pathway, in aneu-MKN45, the expression of molecules in p53 pathway was decreased; HZ08 could increase the expression of p53 down-stream molecules as well as elevate the activity of p53, while inhibiting Mdm2, the major negative regulator of p53; p53 inhibitor Pifithrin-alpha could completely abrogate HZ08's synergism effects, and mimic

cisplatin-resistance on dip-MKN45. Lower p53 pathway expression that attenuates cisplatin-induced apoptosis might be at least partly the reason of cisplatin-resistance occurred in aneuploid MKN45 both in vitro and in vivo; Combination of HZ08 could sensitize cisplatin-induced apoptosis through the activation of the p53 pathway, therefore represented a synergism effect on aneuploid MKN45 cells.

[658]

**TÍTULO / TITLE:** - Role of arterial hypertension as a predictive marker for bevacizumab efficacy in recurrent glioblastoma - a prospective analysis.

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

**REVISTA / JOURNAL:** - Acta Oncol. 2013 Nov 13.

●● [Enlace al texto completo \(gratis o de pago\) 3109/0284186X.2013.852240](#)

**AUTORES / AUTHORS:** - Wagner CC; Held U; Kofmehl R; Battegay E; Zimmerli L; Hofer S

**INSTITUCIÓN / INSTITUTION:** - Division of Internal Medicine, University Hospital Zurich, Zurich, Switzerland.

[659]

**TÍTULO / TITLE:** - Cancer stem-like cell characteristics induced by EB virus-encoded LMP1 contribute to radioresistance in nasopharyngeal carcinoma by suppressing the p53-mediated apoptosis pathway.

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

**REVISTA / JOURNAL:** - Cancer Lett. 2013 Nov 19. pii: S0304-3835(13)00808-2. doi: 10.1016/j.canlet.2013.11.006.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.canlet.2013.11.006](#)

**AUTORES / AUTHORS:** - Yang CF; Peng LX; Huang TJ; Yang GD; Chu QQ; Liang YY; Cao X; Xie P; Zheng LS; Huang HB; Cai MD; Huang JL; Liu RY; Zhu ZY; Qian CN; Huang BJ

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer Chemotherapy, The People's Hospital of Gaozhou, Guangdong Province, China.

**RESUMEN / SUMMARY:** - Emerging evidence confirms that cancer stem cells (CSCs) are responsible for the chemoradioresistance of malignancies. EBV-encoded latent membrane protein 1 (LMP1) is associated with tumor relapse and poor prognosis of nasopharyngeal carcinoma (NPC). However, whether LMP1 induces the development of CSCs and the mechanism by which this rare cell subpopulation leads to radioresistance in NPC remain unclear. In the present study, LMP1-transformed NPC cells showed significant radioresistance compared to the empty vector control. We found that LMP1 up-regulated the expression of several stemness-related genes, increased the cell number of side population (SP) by flow cytometry analysis, enhanced the self-renewal properties of the cells in a spherical culture and enhanced the in vivo tumor initiation ability. We also found that LMP1 positively regulated the expression of the CSC marker CD44. The CD44+/High subpopulation of the LMP1-transformed NPC cells displayed more significant CSC characteristics than the CD44-/Low subpopulation of the LMP1-transformed NPC cells; these characteristics included the upregulation of stemness-related genes, in vitro self-renewal and in vivo tumor initiation ability. Importantly, the CD44+/High subpopulation displayed more

radioresistance than the CD44-/Low subpopulation. Our results also demonstrated that phosphorylation of the DNA damage response (DDR) proteins, ATM, Chk1, Chk2 and p53, was inactivated in the LMP1-induced CD44+/High cells in response to DNA damage, and this was accompanied by a downregulation of the p53-targeted proapoptotic genes, which suggested that the inactivation of the p53-mediated apoptosis pathway was responsible for the radioresistance in the CD44+/High cells. Taken together, we found that LMP1 induced an increase in CSC-like CD44+/High cells, and we determined the molecular mechanism underlying the radioresistance of the LMP1-activated CSCs, highlighting the need of CSC-targeted radiotherapy in EBV-positive NPC.

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[660]

**TÍTULO / TITLE:** - Detection of specific chromosomal aberrations in urine using BCA-1 (oligo-CGH-array) enhances diagnostic sensitivity and predicts the aggressiveness of non-muscle-invasive bladder transitional cell carcinoma.

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

**REVISTA / JOURNAL:** - World J Urol. 2013 Nov 7.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00345-013-1191-3](#)

**AUTORES / AUTHORS:** - Cussenot O; Sighar K; Mohammed M; Hugonin S; Ondet V; Larre S; Lacave R; Roupret M; Cancel-Tassin G

**INSTITUCIÓN / INSTITUTION:** - CeRePP, Paris, France, [olivier.cussenot@wanadoo.fr](mailto:olivier.cussenot@wanadoo.fr).

**RESUMEN / SUMMARY:** - INTRODUCTION: Bladder carcinoma (B-TCC) is the fifth most prevalent carcinoma in the United States (US) or Europe. In addition, B-TCC is the most expensive carcinoma per patient between diagnosis and death, because of its 50-80 % recurrence rate. B-TCC is an optimal carcinoma for which to detect DNA alterations in urine, which is easily obtainable. Chromosomal aberrations in tumors have been closely related to the carcinogenesis process. MATERIAL AND METHODS: We developed a highly specific and sensitive oligo-CGH-array for the diagnosis and follow-up of B-TCC, based on the detection of chromosomal aberrations in urine samples. One hundred and sixty-four urine samples were analyzed. The qualitative results, including chromosomal aberrations, were obtained. Quantitative results are expressed as a percentage of chromosomal alterations on the autosomes. RESULTS: From the urine samples, we were able to differentiate B-TCC from non-malignant conditions with an accuracy of 100 % for patients without history of B-TCC. For follow-up of B-TCC in clinical practice, at least a deletion (8p; 9p; 9q) or a cut-off of >2 % of chromosomal imbalance was considered as a positive test. According to our criteria, 100 % of high-grade tumors were diagnosed, and the sensitivity to predict positive cystoscopy was 95 % (specificity 73 %). A cut-off >9 % was a strong signature of high-grade TCC (odds ratio 53 CI 95 % 7-417; p = 0.0002). CONCLUSION: We developed a sensitive clinical tool for the detection of B-TCC using DNA extracted from patient urine. This tool is also able to identify low-grade B-TCC and identify high-risk patients harboring a high-grade disease.

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[661]

**TÍTULO / TITLE:** - Improving the predictive value of interferon-gamma release assays: do our methods go far enough? [Editorial].

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

**REVISTA / JOURNAL:** - Int J Tuberc Lung Dis. 2013 Dec;17(12):1516. doi: 10.5588/ijtld.13.0705.

●● Enlace al texto completo (gratis o de pago) [5588/ijtld.13.0705](#)

**AUTORES / AUTHORS:** - Kik SV; Rangaka MX

**INSTITUCIÓN / INSTITUTION:** - McGill International TB Centre & Department of Epidemiology & Biostatistics, McGill University, Montreal, QC, Canada.

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[662]

**TÍTULO / TITLE:** - The Up-Regulation of Histone Deacetylase 8 Promotes Proliferation and Inhibits Apoptosis in Hepatocellular Carcinoma.

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

**REVISTA / JOURNAL:** - Dig Dis Sci. 2013 Sep 28.

●● Enlace al texto completo (gratis o de pago) [1007/s10620-013-2867-7](#)

**AUTORES / AUTHORS:** - Wu J; Du C; Lv Z; Ding C; Cheng J; Xie H; Zhou L; Zheng S

**INSTITUCIÓN / INSTITUTION:** - Department of Hepatobiliary Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Histone deacetylase 8 (HDAC8), a member of class I HDACs, has been reported to be involved in transcriptional regulation, cell cycle progression, and developmental events, and several studies have shown that HDAC8 plays a critical role in tumorigenesis. However, the expression level and the potential role of HDAC8 in hepatocellular carcinoma (HCC) remain unclear. AIM: The purpose of this study was to investigate protein expression of HDAC8 in HCC tissues and the effects of HDAC8 knockdown on the proliferation and apoptosis of liver cancer cells, and to explore the possible mechanisms. METHODS: First, we used quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR), immunohistochemical staining, and western blot to examine the mRNA and protein expression of HDAC8 in HCC cell lines and tissues. Then, we assessed the correlation between clinicopathological parameters and the protein expression of HDAC8. Furthermore, we employed the interfering RNA method to explore the potential role of HDAC8 in HCC progression in vitro. RESULTS: Our results showed that expression of HDAC8 was significantly up-regulated both in HCC cell lines and tumor tissues compared to human normal liver cell line LO2 and corresponding non-tumor tissues. Moreover, we found that HDAC8 knockdown could dramatically inhibit HCC cell proliferation and enhance the apoptosis rate in vitro. Western blot revealed that intrinsic apoptotic pathway proteins, including BAX, BAD, and BAK, were elevated after HDAC8 knockdown. The cleavage of caspase-3 and PARP, which are downstream of intrinsic apoptotic pathway, were also enhanced. In addition, suppression of HDAC8 also elevated the expression of p53 and acetylation of p53 at Lys382, whereas the acetylation of p53 at Lys373 did not change. CONCLUSIONS: Our study revealed that HDAC8 was overexpressed in HCC. HDAC8 knockdown suppresses tumor growth and enhances apoptosis in HCC via elevating the expression of p53 and acetylation of p53 at Lys382. HDAC8 might serve as a potential therapeutic target in HCC.

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[663]

**TÍTULO / TITLE:** - Combination of the FGFR4 inhibitor PD173074 and 5-fluorouracil reduces proliferation and promotes apoptosis in gastric cancer.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2013 Dec;30(6):2777-84. doi: 10.3892/or.2013.2796. Epub 2013 Oct 11.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2796](#)

**AUTORES / AUTHORS:** - Ye YW; Hu S; Shi YQ; Zhang XF; Zhou Y; Zhao CL; Wang GJ; Wen JG; Zong H

**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China.

**RESUMEN / SUMMARY:** - Our previous findings revealed that FGFR4 may be a novel therapeutic target for gastric cancer. The aim of the present study was to explore the effects of a combination of PD173074 (PD) and 5-fluorouracil (5-Fu) on the biological behavior of gastric cancer cell lines and the relevant mechanisms involved. MKN45, a gastric cancer cell line, was treated with each single agent alone or a combination of FGF19, PD and 5-Fu. Then, a series of functional assays were performed using CCK-8 assay and flow cytometry. Western blot analysis was used to determine the expression of signaling pathway and downstream-related molecules in the MKN45 cells following the different treatments. As the concentration of PD and 5-Fu increased, the cell viability gradually decreased; the viability of the combination group was less than the viability following single administration. Western blot analysis showed that FGFR4 expression was weak in the 5-Fu-treated groups when compared with the control. PD markedly increased the apoptosis rate of MKN45 cells when compared to the control; the apoptosis rate in the cells treated with the combination of PD and 5-Fu was higher than that in the cells following single treatment. Furthermore, PD reduced the expression of p-ERK and Bcl-xl and increased caspase-3 expression. Inhibition of the activity of FGFR4 may be the main mechanisms of PD effect while 5-Fu reduced FGFR4 expression. Furthermore, the effects of the combination of 5-Fu and PD in inhibiting proliferation, increasing apoptosis and arresting cell cycle were superior to these effects following the single agent treatments, suggesting that the two drugs applied in combination may contribute to the effective treatment of gastric cancer.

[664]

**TÍTULO / TITLE:** - Purified vitexin compound 1 induces apoptosis through activation of FOXO3a in hepatocellular carcinoma.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):488-96. doi: 10.3892/or.2013.2855. Epub 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2855](#)

**AUTORES / AUTHORS:** - Wang JG; Zheng XX; Zeng GY; Zhou YJ; Yuan H

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiology, The Third Xiangya Hospital of Central South University, Changsha, Hunan 410013, P.R. China.

**RESUMEN / SUMMARY:** - We previously reported that purified vitexin compound 1 (VB1, a neolignan from the seed of Chinese herb Vitex negundo) exhibited antitumor activity in cancer cell lines and xenograft models. In the present study, we examined the molecular mechanisms by which activation of the FOXO3a transcription factor mediated VB1-induced apoptosis in hepatocellular carcinoma (HCC) cells. The effects

of VB1 on the proliferation of HCC cell lines HepG2, Hep3B, Huh-7 and human embryo liver L-02 cells were investigated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Apoptotic death in HepG2 cells was examined using an enzyme-linked immunosorbent assay (ELISA) detection kit, flow cytometry after propidium iodide (PI) staining, and by DNA agarose gel electrophoresis. Caspase activity was measured using ELISA. The AKT/FOXO3a and ERK/FOXO3a pathways were analyzed using western blotting. VB1 inhibited human HCC cell proliferation in a concentration-dependent manner and increased the percentage of sub-G1 population HepG2 cells. Histone/DNA fragmentation and active caspase-3, -8 and -9 levels increased in a concentration-dependent manner and a DNA ladder was formed. The phosphorylation of AKT and ERK1/2 were inhibited and FOXO3a transcription factor was activated, resulting in apoptotic death. Knockdown of AKT1 by small interfering RNA (siRNA) and the MEK1/2 inhibitor, PD98059, enhanced VB1-induced apoptosis and FOXO3a transcriptional activity. Suppression of FOXO3a expression by siRNA inhibited VB1-induced apoptosis. VB1 induced expression of Bim, TRAIL, DR4 and DR5. Activation of the FOXO3a transcription factor appears to mediate pro-apoptotic effects of VB1 by inhibiting the AKT and ERK pathways.

[665]

**TÍTULO / TITLE:** - CD8+ lymphocytes and apoptosis in typical and atypical medullary carcinomas of the breast.

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

**REVISTA / JOURNAL:** - Immunol Lett. 2013 Nov-Dec;156(1-2):123-6. doi: 10.1016/j.imlet.2013.10.001. Epub 2013 Oct 11.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.imlet.2013.10.001](#)

**AUTORES / AUTHORS:** - Nurlaila I; Telisinghe PU; Ramasamy R

**INSTITUCIÓN / INSTITUTION:** - Institute of Health Sciences, Universiti Brunei Darussalam, Gadong, Brunei Darussalam.

**RESUMEN / SUMMARY:** - Medullary breast carcinoma (MBC) is a form of ductal invasive carcinoma (DIC) characterized by an abundant infiltration of the tumour by lymphocytes. MBC has been classified histologically into typical medullary carcinoma (TMC) and atypical medullary carcinoma (AMC), with TMC having a better prognosis than AMC and other DIC. The distribution of CD8+ lymphocytes within tumour nests and lymphocyte tracts, and apoptosis in lymphocytes and tumour cells within tumour nests, were studied in archived formalin fixed and paraffin embedded tissues of TMC and AMC. CD8+ lymphocytes tend to accumulate along the margins of lymphocyte tracts that adjoin tumour nests. There were significantly more CD8+ lymphocytes within tumour nests of TMC than AMC. TMC also tended to have more CD8+ lymphocytes within lymphocyte tracts than AMC. Apoptosis of lymphocytes in contact with tumour cells and of tumour cells in contact with lymphocytes was observed in both AMC and TMC within tumour nests but differences in the proportions of apoptotic tumour cells and lymphocytes between the two tumour types could not be established. The findings are consistent with CD8+ cytotoxic lymphocyte-mediated immunity contributing to the more favourable prognosis for TMC compared to AMC.

[666]

**TÍTULO / TITLE:** - Intralesional interferon alfa-2b for refractory, recurrent squamous cell carcinoma of the face.

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

**REVISTA / JOURNAL:** - J Am Acad Dermatol. 2013 Dec;69(6):1070-2. doi: 10.1016/j.jaad.2013.02.032.

●● Enlace al texto completo (gratis o de pago) [1016/j.jaad.2013.02.032](#)

**AUTORES / AUTHORS:** - Hanlon A; Kim J; Leffell DJ

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology, Section of Cutaneous Oncology and Dermatologic Surgery, Yale University School of Medicine, New Haven, Connecticut. Electronic address: [allison.hanlon@yale.edu](mailto:allison.hanlon@yale.edu).

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[667]

**TÍTULO / TITLE:** - Primary Cutaneous Anaplastic Large Cell Lymphoma with Angioinvasive Features and Cytotoxic Phenotype: A Rare Lymphoma Variant within the Spectrum of CD30+ Lymphoproliferative Disorders.

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

**REVISTA / JOURNAL:** - Dermatology. 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [1159/000355479](#)

**AUTORES / AUTHORS:** - Kempf W; Kazakov DV; Paredes BE; Laeng HR; Palmedo G; Kutzner H

**INSTITUCIÓN / INSTITUTION:** - Kempf und Pfaltz, Histologische Diagnostik, University Hospital, Zurich, Switzerland.

**RESUMEN / SUMMARY:** - Background: Primary cutaneous anaplastic large cell lymphoma (PCALCL) presents with solitary or grouped exophytic tumors and cohesive infiltrates of large CD30+ T cells. Objective: To report an angioinvasive variant of PCALCL. Methods: Retrospective analysis of clinicopathological features of this variant. Results: The group consisted of six patients (median age 46 years) with a solitary flat necrotic lesion preferentially located on the upper extremity. Histologically, there were angiocentric and angiodestructive infiltrates of medium-sized to large pleomorphic and anaplastic cells co-expressing CD30 and CD8. Five patients were treated with surgical excision and one patient with radiotherapy. A relapse was observed in one patient with spontaneous regression of the lesions suggesting a link to the recently described angioinvasive lymphomatoid papulosis (type E). All patients were alive without evidence of disease after a median follow-up of 31 months (range 15-96), indicating an excellent prognosis. Conclusions: The angioinvasive variant of PCALCL is rare but distinctive and prone to misinterpretation as aggressive lymphoma due to its histological features. © 2013 S. Karger AG, Basel.

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[668]

**TÍTULO / TITLE:** - Effects of tetrandrine on glioma cell malignant phenotype via inhibition of ADAM17.

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

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Nov 3.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1293-y](#)

**AUTORES / AUTHORS:** - Wu Z; Wang G; Xu S; Li Y; Tian Y; Niu H; Yuan F; Zhou F; Hao Z; Zheng Y; Li Q; Wang J

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, The 2<sup>nd</sup> Affiliated Hospital, Harbin Medical University, Harbin, 150086, China.

**RESUMEN / SUMMARY:** - Tetrandrine (TET), a bisbenzylisoquinoline alkaloid isolated from the root of Hang-Fang-Chi (*Stephania tetrandra* S. Moore), exhibits broad pharmacological effects, including antitumor activity in various malignant neoplasms. Recently, the beneficial effects of TET on cytotoxicity towards tumor cells, radiosensitization, circumventing multidrug resistance, normal tissue radioprotection, and antiangiogenesis have been examined extensively. However, the potential molecular mechanisms of the effect on glioma of TET are yet unknown. This study is explored to evaluate whether TET can inhibit cell proliferation, invasion, and the possible underlying mechanisms in glioma U87 cell. In the present study, cell proliferation was determined by using the Cell Counting Kit-8 (CCK-8) viability assay. The invasion and migration were evaluated by means of wound-scratch assay and Matrigel-Transwell methods. The mRNA expression and protein expression of ADAM metalloproteinase domain 17 (ADAM17) in glioma cell lines and glioma samples were determined by reverse transcription-polymerase chain reaction (RT-PCR) and Western blotting, respectively. Moreover, the expression of epidermal growth factor receptor (EGFR)/p-EGFR and AKT/p-AKT was studied to clarify the molecular mechanism. Our results suggested that TET inhibited cell proliferation in a dose- and time-dependent manner, and cell migration and invasion in vitro. In addition, our results indicated that ADAM17 expression significantly increased in glioma compared to nontumored human brain tissue and according to the histopathological grade of glioma. Western blot analysis showed that protein expressions of ADAM17, p-EGFR, and p-AKT were inhibited by TET in U87 cells. These data also suggest that suppression of ADAM17 and downregulation of EGFR-phosphoinositide-3-kinase (PI3K)-AKT signaling pathways may contribute to TET-induced decrease of proliferation, migration, and invasiveness.

[669]

**TÍTULO / TITLE:** - Quantification of HBG mRNA in primary erythroid cultures: prediction of the response to hydroxyurea in sickle cell and beta-thalassemia.

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

**REVISTA / JOURNAL:** - Eur J Haematol. 2013 Sep 20. doi: 10.1111/ejh.12204.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ejh.12204](#)

**AUTORES / AUTHORS:** - Pecoraro A; Rigano P; Troia A; Calzolari R; Scazzone C; Maggio A; Steinberg MH; Marzo RD

**INSTITUCIÓN / INSTITUTION:** - Dipartimento di Oncologia ed Ematologia, U.O.C. Ematologia per le Malattie Rare del Sangue e degli Organi Ematopoietici, A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy.

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVE: Increased expression of fetal hemoglobin (HbF) may ameliorate the clinical course of hemoglobinopathies like sickle cell disease (SCD) and beta-thalassemia. Hydroxyurea (HU) can stimulate HbF production in these diseases but the response is highly variable indicating the utility of developing an in vitro test to predict the patient's response to HU. We assessed whether the HbF response of patients with SCD and thalassemia intermedia (TI) to HU correlates with HBG (both gamma-globin genes) expression in their cultured erythroid progenitors following exposure to HU. PATIENTS AND METHODS: We exposed

primary erythroid cultures from peripheral blood mononuclear cells from 30 patients with SCD and 15 with TI to HU and measured HBG mRNA by real-time quantitative PCR. The same patients were then treated with HU and their HbF response after treatment with a stable dose of HU was compared with the mRNA results in cultured cells. RESULTS AND CONCLUSION: The fold increase in HBG mRNA in erythroid progenitors was similar to the fold increase in HbF in vivo. Quantification of HBG mRNA in erythroid progenitor cell cultures from patients with SCD and TI is predictive of their clinical response to HU.

[670]

**TÍTULO / TITLE:** - Human cancer cell line microRNAs associated with in vitro sensitivity to paclitaxel.

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

**REVISTA / JOURNAL:** - Oncol Rep. 2014 Jan;31(1):376-83. doi: 10.3892/or.2013.2847. Epub 2013 Nov 13.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2847](#)

**AUTORES / AUTHORS:** - Chen N; Chon HS; Xiong Y; Marchion DC; Judson PL; Hakam A; Gonzalez-Bosquet J; Permut-Wey J; Wenham RM; Apte SM; Cheng JQ; Sellers TA; Lancaster JM

**INSTITUCIÓN / INSTITUTION:** - Department of Women's Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA.

**RESUMEN / SUMMARY:** - Paclitaxel is a mainstay of treatment for many solid tumors, and frequently, clinical outcome is influenced by paclitaxel sensitivity. Despite this, our understanding of the molecular basis of paclitaxel response is incomplete. Recently, it has been shown that microRNAs (miRNAs) influence messenger RNA (mRNA) transcriptional control and can contribute to human carcinogenesis. In the present study, our objective was to identify miRNAs associated with cancer cell line response to paclitaxel and to evaluate these miRNAs as therapeutic targets to increase paclitaxel sensitivity. We measured the expression of 335 unique miRNAs in 40 human cancer cell lines selected from the NCI panel. We then integrated miRNA expression data with publicly available paclitaxel-sensitivity (GI50) data for each of the 40 cell lines to identify miRNAs associated with paclitaxel sensitivity. Ovarian cancer cell lines with differential miRNA expression and paclitaxel sensitivity were transiently transfected with miRNA precursors and inhibitors, and the effects on in vitro cell paclitaxel sensitivity were evaluated. Pearson's correlation identified 2 miRNAs (miR-367 and miR-30a-5p) associated with the NCI40 cell line in vitro paclitaxel response ( $P < 0.0003$ ). Ovarian cancer cells were selected based on the association between paclitaxel sensitivity and miR-367/miR-30a-5p expression. Overexpression of miR-367 in the paclitaxel-sensitive cells [PA1; IC50, 1.69 nM, high miR-367 (2.997), low miR-30a-5p (-0.323)] further increased paclitaxel sensitivity, whereas miR-367 depletion decreased paclitaxel sensitivity. In contrast, overexpression and depletion of miR-30a-5p in the paclitaxel-resistant cells [OVCAR4; IC50, 17.8 nM, low miR-367 (-0.640), high miR-30a-5p (3.270)] decreased and increased paclitaxel sensitivity, respectively. We identified and successfully targeted miRNAs associated with human cancer cell line response to paclitaxel. Our strategy of integrating in vitro miRNA expression and drug sensitivity data may not only aid in the characterization of determinants of drug

response but also in the identification of novel therapeutic targets to increase activity of existing therapeutics.

[671]

**TÍTULO / TITLE:** - Syndrome of Inappropriate Secretion of Antidiuretic Hormone due to Selective Serotonin Reuptake Inhibitors After Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater: Case Report.

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

**REVISTA / JOURNAL:** - Int Surg. 2013 Oct-Dec;98(4):289-91. doi: 10.9738/INTSURG-D-13-00032.1.

●● Enlace al texto completo (gratis o de pago) [9738/INTSURG-D-13-00032.1](#)

**AUTORES / AUTHORS:** - Iwase R; Shiba H; Gocho T; Futagawa Y; Wakiyama S; Ishida Y; Misawa T; Yanaga K

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan.

**RESUMEN / SUMMARY:** - Abstract A 68-year-old man underwent pancreaticoduodenectomy with lymph nodes dissection for carcinoma of the ampulla of Vater. The patient had anxiety neurosis and had been treated with a selective serotonin reuptake inhibitor (SSRI). Postoperatively, SSRI was resumed on postoperative day 2. His serum sodium concentration gradually decreased, and the patient was given a sodium supplement. However, 11 days after the operation, laboratory findings included serum sodium concentration of 117 mEq/L, serum vasopressin of 2.0 pg/mL, plasma osmolality of 238 mOsm/kg, urine osmolality of 645 mOsm/kg, urine sodium concentration of 66 mEq/L, serum creatinine concentration of 0.54 mg/dL, and serum cortisol concentration of 29.1 µg/dL. With a diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH), the anti-anxiety neurosis medication was changed from the SSRI to another type of drug. After switching the medication, the patient made a satisfactory recovery with normalization of serum sodium by postoperative day 20.

[672]

**TÍTULO / TITLE:** - Thermally targeted p21 peptide enhances bortezomib cytotoxicity in androgen-independent prostate cancer cell lines.

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

**REVISTA / JOURNAL:** - Anticancer Drugs. 2013 Oct 9.

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

[1097/CAD.0000000000000036](#)

**AUTORES / AUTHORS:** - Mikecin AM; Walker LR; Kuna M; Raucher D

**INSTITUCIÓN / INSTITUTION:** - aDepartment of Biochemistry, University of Mississippi Medical Center, Jackson, Mississippi, USA bDepartment of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia.

**RESUMEN / SUMMARY:** - Prostate cancer remains one of the most common malignancies in men. Besides surgical resection, treatments for prostate cancer include hormone therapy, chemotherapy, and radiation therapy. Advancement of prostate cancer to an androgen-independent state limits the potential of conventional therapeutic approaches. Bortezomib, an FDA-approved proteasomal inhibitor for the

treatment of myeloid leukemia, has been shown to have a positive effect on the inhibition of prostate cancer growth. Unfortunately, bortezomib has a very narrow therapeutic window, which can lead to severe side effects. Elastin-like polypeptide (ELP) is a genetically engineered, thermally responsive macromolecular carrier that enables a targeted delivery of the bound molecule because of its soluble property under normal physiologic conditions. In addition, ELP aggregates in response to mild hyperthermia. Using ELP as a carrier, it is possible to improve the pharmacological properties of the therapeutic drug as well as reduce toxicity in normal tissues. In this work, we have investigated the combination treatment of androgen-independent prostate cancer cells with bortezomib and the C-terminal part of the p21 protein bound to the ELP carrier. We have found that combination treatment with bortezomib and ELP-bound p21 protein leads to increased cell cycle arrest as well as apoptosis with respect to single treatments. We believe that this approach represents a promising direction for the treatment of androgen-independent prostate cancer.

[673]

**TÍTULO / TITLE:** - Role of the aromatase inhibitor letrozole in the management of uterine leiomyomas in premenopausal women.

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

**REVISTA / JOURNAL:** - Eur J Obstet Gynecol Reprod Biol. 2013 Sep 20. pii: S0301-2115(13)00460-0. doi: 10.1016/j.ejogrb.2013.09.010.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ejogrb.2013.09.010](#)

**AUTORES / AUTHORS:** - Duhan N; Madaan S; Sen J

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics & Gynecology, Pt. B.D. Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India. Electronic address: [nkadian@gmail.com](mailto:nkadian@gmail.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Uterine myomas are benign tumours affecting 20-40% women. Various medical and surgical therapeutic options are available but the search for an ideal medical option continues. Aromatase inhibitors have recently been reported to have a potential role in the management of oestrogen-dependent conditions like endometriosis and leiomyoma. OBJECTIVE: To evaluate the effect of letrozole on uterine myoma size and symptomatology in perimenopausal women. STUDY DESIGN: Prospective interventional study conducted on 30 premenopausal women aged between 30 and 55 years with menstrual or pressure symptoms and having a single intrauterine myoma of size 4cm or more with or without one or more additional myomata each of size 2cm or less. They received tablet letrozole 2.5mg a day for 12 weeks, and the effect of the drug on myoma size and volume and symptomatology was studied along with the adverse effect profile and patient satisfaction. RESULTS: The mean myoma size reduced from 5.4+/-1.3cm to 4.3+/-0.9cm (p<0.05) and the myoma volume exhibited a reduction of 52.45% (p=0.00) at the end of 3 months. The symptomatology score showed a significant improvement that persisted up to 3 months after cessation of therapy. No significant effect was observed on lipid profile, serum estradiol, progesterone, testosterone and FSH and LH levels during the therapy. Nausea and hot flushes were the main adverse effects observed and were self-limiting. CONCLUSION: Letrozole significantly reduces myoma size and volume and also improves the associated symptoms. It has a good adverse

effect profile and appears to be a promising medical option for management of uterine myomas.

[674]

**TÍTULO / TITLE:** - Lead enhances fluoride influence on apoptosis processes in liver cell line HepG2.

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

**REVISTA / JOURNAL:** - Toxicol Ind Health. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1177/0748233713502843](https://doi.org/10.1177/0748233713502843)

**AUTORES / AUTHORS:** - Gutowska I; Baranowska-Bosiacka I; Siwiec E; Szczuko M; Kolasa A; Kondarewicz A; Rybicka M; Dunaj-Stanczyk M; Wiernicki I; Chlubek D; Stachowska E

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Human Nutrition, Pomeranian Medical University, Szczecin, Poland.

**RESUMEN / SUMMARY:** - Chronic long-term exposure to high levels of fluoride leads to fluorosis, manifested by skeletal fluorosis and damage to internal organs, including kidneys, liver, parathyroid glands, and brain. Excess fluoride can also cause DNA damage, trigger apoptosis, and change cell cycle. The effect of fluoride may be exacerbated by lead (Pb), a potent inhibitor of many enzymes and a factor causing apoptosis, still present in the environment in excessive amounts. Therefore, in this study, we investigated the effects of sodium fluoride (NaF) and/or lead acetate (PbAc) on development of apoptosis, cell vitality, and proliferation in the liver cell line HepG2. We examined hepatocytes from the liver cell line HepG2, incubated for 48 h with NaF, PbAc, and their mixture (NaF + PbAc), and used for measuring apoptosis, index of proliferation, and vitality of cells. Incubation of the hepatocytes with NaF or PbAc increased apoptosis, more when fluoride and Pb were used simultaneously. Vitality of the cells depended on the compound used and its concentration. Proliferation slightly increased and then decreased in a high fluoride environment; it decreased significantly after addition of Pb in a dose-dependent manner. When used together, fluoride inhibited the decreasing effect of Pb on cell proliferation.

[675]

**TÍTULO / TITLE:** - MicroRNA-29a upregulates MMP2 in oral squamous cell carcinoma to promote cancer invasion and anti-apoptosis.

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

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Oct 18. pii: S0753-3322(13)00117-0. doi: 10.1016/j.biopha.2013.10.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.biopha.2013.10.005](https://doi.org/10.1016/j.biopha.2013.10.005)

**AUTORES / AUTHORS:** - Lu L; Xue X; Lan J; Gao Y; Xiong Z; Zhang H; Jiang W; Song W; Zhi Q

**INSTITUCIÓN / INSTITUTION:** - The Stomatological Hospital Affiliated to Soochow University, Suzhou, 215000 JiangSu Province, China.

**RESUMEN / SUMMARY:** - Abnormal microRNA expression is a common and important feature of human malignancies. Matrix metalloproteinase 2 (MMP2), which has been reported in several cancers, plays important roles in cancer progression. However, the microRNA regulatory mechanism on MMP2 expression remains unclear. In this study,

we first detected MMP2 and microRNA-29a (miR-29a) expression in oral squamous carcinoma (OSCC) specimens, which showed that MMP2 was higher in OSCC cancer tissues than adjacent tissues but that miR-29a was lower in OSCC cancer tissues than adjacent tissues. Then, we confirmed that miR-29a, which directly targeted 3'-UTR of MMP2 gene, negatively regulated MMP2 expression by miR-29a transfection and luciferase reporter assay. Exogenous overexpression of miR-29a inhibited OSCC cell invasion and anti-apoptosis significantly in vitro. Whereas, knockdown of miR-29a promoted OSCC cell invasion and induced drug-resistance in vitro. This study suggests that miR-29a plays an inhibiting role in the progression of OSCC, which may be a potentially therapeutic approach in the future.

[676]

**TÍTULO / TITLE:** - Lobaplatin arrests cell cycle progression, induces apoptosis and alters the proteome in human cervical cancer cell Line CaSki.

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

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Oct 18. pii: S0753-3322(13)00116-9. doi: 10.1016/j.biopha.2013.10.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.biopha.2013.10.004](#)

**AUTORES / AUTHORS:** - Li X; Ran L; Fang W; Wang D

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical laboratory, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. Electronic address: [lixiaoqin467@126.com](mailto:lixiaoqin467@126.com).

**RESUMEN / SUMMARY:** - Cervical cancer is one of the most common gynecologic tumors. There is an upward trend in the incidence. The objective of this research was to explore the effect of lobaplatin on cervical cancer CaSki cells proliferation, cell cycle and apoptosis and analysis of the differential expressed proteins of CaSki cells after exposed to lobaplatin. Our findings have shown that lobaplatin inhibits cell proliferations in human cervical cancer CaSki cells in dose- and time-dependent manner. Flow cytometry assay confirmed that lobaplatin affected cervical cancer cell survival by blocking cell cycle progression in S phase and G0/G1 phase and inducing apoptosis in dose- and time-dependent manner. Lobaplatin treatment reduced polypyrimidine tract-binding protein 2, ribose-phosphate pyrophosphokinase, hypothetical protein, terminal uridylyltransferase 7, ubiquitin specific protease 16 and heterogeneous nuclear ribonucleoprotein A2/B1 expression and increase zinc finger protein 91, zinc finger protein, C-X-C motif chemokine 10 precursor, stromal cell protein and laminin subunit alpha-4 expression. Some of the differentially expressed proteins may be associated with antitumor effect of lobaplatin. Lobaplatin showed a good antitumour activity in in vitro models of human cervical cancer cells. These results indicate that lobaplatin could be an effective chemotherapeutic agent in human cervical cancer treatment by inducing apoptosis, cell cycle arrest and changing many kinds of protein molecule expression level.

[677]

**TÍTULO / TITLE:** - Induction of cancer cell death by apoptosis and slow release of 5-fluoracil from metal-organic frameworks Cu-BTC.

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

**REVISTA / JOURNAL:** - Biomed Pharmacother. 2013 Oct;67(8):707-13. doi: 10.1016/j.biopha.2013.06.003. Epub 2013 Jul 2.

●● Enlace al texto completo (gratis o de pago) [1016/j.biopha.2013.06.003](https://doi.org/10.1016/j.biopha.2013.06.003)

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**RESUMEN / SUMMARY:** - This study aimed to evaluate the mechanism associated with cytotoxic activity displayed by the drug 5-fluorouracil incorporated in Cu-BTC MOF and its slow delivery from the Cu-BTC MOF. Structural characterization encompasses elemental analysis (CHNS), differential scanning calorimetry (DSC), thermogravimetric analysis (TG/DTG), Fourier transform infrared (FT-IR) and X-ray diffraction (XRD) was performed to verify the process of association between the drug 5-FU and Cu-BTC MOF. Flow cytometry was done to indicate that apoptosis is the mechanism responsible for the cell death. The release profile of the drug 5-FU from Cu-BTC MOF for 48 hours was obnoxious. Also, the anti-inflammatory activity was evaluated by the peritonitis testing and the production of nitric oxide and pro-inflammatory cytokines were measured. The chemical characterization of the material indicated the presence of drug associated with the coordination network in a proportion of 0.82g 5-FU per 1.0g of Cu-BTC MOF. The cytotoxic tests were carried out against four cell lines: NCI-H292, MCF-7, HT29 and HL60. The Cu-BTC MOF associated drug was extremely cytotoxic against the human breast cancer adenocarcinoma (MCF-7) cell line and against human acute promyelocytic leukemia cells (HL60), cancer cells were killed by apoptosis mechanisms. The drug demonstrated a slow release profile where 82% of the drug was released in 48 hours. The results indicated that the drug incorporated in Cu-BTC MOF decreased significantly the number of leukocytes in the peritoneal cavity of rodents as well as reduced levels of cytokines and nitric oxide production.

[678]

**TÍTULO / TITLE:** - Predictive biomarkers in adult gliomas: the present and the future.

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

**REVISTA / JOURNAL:** - Curr Opin Oncol. 2013 Nov;25(6):689-94. doi: 10.1097/CCO.0000000000000002.

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

[1097/CCO.0000000000000002](https://doi.org/10.1097/CCO.0000000000000002)

**AUTORES / AUTHORS:** - Thomas L; Di Stefano AL; Ducray F

**INSTITUCIÓN / INSTITUTION:** - aService de Neuro-Oncologie, Hopital Neurologique, Hospices Civils de Lyon bUniversite Pierre et Marie Curie-Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle epiniere (CRICM), UMR-S975, Paris cINSERM, U1028; CNRS, UMR5292; Lyon Neuroscience Research Center, Neuro-Oncology and Neuro-Inflammation Team, Universite Claude Bernard Lyon 1, Lyon, France.

**RESUMEN / SUMMARY:** - PURPOSE OF REVIEW: This review summarizes recent studies on the predictive value of molecular markers in adult gliomas, including 1p/19q codeletion, MGMT methylation, IDH mutation and markers identified using omics and next-generation sequencing studies. RECENT FINDINGS: The long-term results of the Radiation Therapy Oncology Group and European Organization for Research and

Treatment of Cancer trials in anaplastic oligodendroglial glioma have shown that the 1p/19q codeletion predicts an overall survival benefit from early PCV (procarbazine CCNU vincristine) chemotherapy. This benefit can also be predicted using gene expression-based molecular subtypes of gliomas while the predictive value of the IDH mutation in this context requires further study. In elderly patients with glioblastoma, the analysis of MGMT methylation status in two phase III trials suggests that this alteration may guide treatment decisions; however, this finding still needs confirmation in prospective studies. Omics and next-generation sequencing studies have identified additional potential predictive markers. In particular, IDH mutations, BRAF V600E mutations and FGFR gene fusions might predict efficacy of therapies targeted against these alterations. SUMMARY: Currently, the 1p/19q codeletion is the only well established predictive marker with clinical utility. However, it is likely that other molecular markers such as MGMT methylation, IDH mutation and those identified using omics and next-generation sequencing studies will further guide treatment decisions in adult gliomas.

[679]

**TÍTULO / TITLE:** - MicroRNA-191 correlates with poor prognosis of colorectal carcinoma and plays multiple roles by targeting tissue inhibitor of metalloprotease 3.

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

**REVISTA / JOURNAL:** - Neoplasma. 2014;61(1):27-34.

**AUTORES / AUTHORS:** - Qin S; Zhu Y; Ai F; Li Y; Bai B; Yao W; Dong L

**RESUMEN / SUMMARY:** - MicroRNA-191 (miR-191) is reported to be overexpressed in colorectal carcinoma (CRC), but the role of miR-191 in CRC progress remained unclear. This study demonstrated that High miR-191 expression was associated with clinical stage, lymph node metastasis, liver metastasis and depth of tumor invasion. Kaplan-Meier analysis indicated that patients with high miR-191 expression had a poor overall survival. Moreover, multivariate analysis showed that miR-191 was an independent prognostic factor in patients with CRC. Furthermore, we found that tissue inhibitor of metalloprotease 3 (TIMP3) was a direct target of miR-191 in colorectal cancer SW620 cells. TIMP3 downregulation mediated by miR-191 activated matrix metalloproteinases (MMPs) and thus promoted invasiveness of cancer cells. Anti-miR-191 could attenuate the invasiveness, suppress proliferation and induce apoptosis by restoring TIMP3 expression. Our results suggested that miR-191 might be a potential diagnostic and therapeutic target in patients with colorectal cancer. Keywords: microRNA-191; colorectal carcinoma; prognosis; tissue inhibitor of metalloprotease 3.

[680]

**TÍTULO / TITLE:** - Activity of Outpatient Intravenous Interleukin-2 and Famotidine in Metastatic Clear Cell Kidney Cancer.

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

**REVISTA / JOURNAL:** - Cancer Biother Radiopharm. 2013 Nov 19.

●● [Enlace al texto completo \(gratis o de pago\) 1089/cbr.2013.1555](#)

**AUTORES / AUTHORS:** - Quan WD Jr; Quan FM

**INSTITUCIÓN / INSTITUTION:** - 1 Department of Medical Oncology, Western Regional Medical Center, Goodyear, Arizona.

**RESUMEN / SUMMARY:** - Abstract Outpatient daily intravenous infusions of interleukin-2 (IL-2) have been developed to maintain anticancer activity and decrease toxicity of this agent against kidney cancer. Lymphokine activated killer cell (LAK) numbers are increased with these IL-2 schedules. Famotidine may enhance the LAK activity by increasing IL-2 internalization by the IL-2 receptor on lymphocytes. Fifteen patients with metastatic clear cell kidney cancer received IL-2 18 million IU/M2 intravenously over 15-30 minutes preceded by famotidine 20 mg IV daily for 3 days for 6 consecutive weeks as outpatients. Cycles were repeated every 8 weeks. Patient characteristics were seven males/eight females, median age 59 (range: 28-70), median Eastern Cooperative Oncology Group (ECOG) performance status-1; common metastatic sites were lungs (14), lymph nodes (9), liver (4), bone (4), and pancreas (4). Prior systemic therapies were oral tyrosine kinase inhibitor (8), IL-2 (6), and mTor inhibitor (2). Most common toxicities were rigors, arthralgia/myalgia, nausea/emesis, fever, and hypotension. All episodes of hypotension were reversible with intravenous fluid. No patients required hospitalization due to toxicity. One complete response (7%) and four partial responses (26%) were seen (total response rate=33%; 95% confidence interval: 15%-59%). Responses occurred in the lungs, liver, lymph nodes, and bone. Outpatient intravenous IL-2 with famotidine has activity in metastatic clear cell kidney cancer.

[681]

**TÍTULO / TITLE:** - Anti-proliferative and pro-apoptotic effects from sequenced combinations of andrographolide and cisplatin on ovarian cancer cell lines.

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

**REVISTA / JOURNAL:** - Anticancer Res. 2013 Oct;33(10):4365-71.

**AUTORES / AUTHORS:** - Yunos NM; Mutalip SS; Jauri MH; Yu JQ; Huq F

**INSTITUCIÓN / INSTITUTION:** - Discipline of Biomedical Science, The University of Sydney, 75 East Street, Lidcombe NSW 1825, Australia. [Fazlul.huq@sydney.edu.au](mailto:Fazlul.huq@sydney.edu.au) and Nurhanan Murni Yunos, Drug Discovery Centre, Natural Products Division, Forest Research Institute Malaysia, Kepong, Selangor, Malaysia. E-mail: [hanan@frim.gov.my](mailto:hanan@frim.gov.my).

**RESUMEN / SUMMARY:** - Andrographolide (Andro) is a diterpenoid that is isolated from *Andrographis paniculata* and reported to be active against several cancer cell lines. However, few in-depth studies have been carried out on its effects on ovarian cancer cell lines alone or in combination with cisplatin (Cis), which is commonly used to treat ovarian cancer. The aim of this study was to determine the anti-proliferative and apoptotic effects of Andro administered alone and in combination with Cis in the ovarian A2780 and A2780(cisR) cancer cell lines using five different sequences of administration (Cis/Andro h): 0/0h, 4/0 h, 0/4 h, 24/0 h and 0/24 h. The results were evaluated in terms of medium-effect dose (Dm) and combination indices (CI) using the CalcuSyn software. Unlike Cis, whose activity was lower in the resistant A2780(cisR) cell line than in the parent A2780 cell line, Andro was found to be three times more active in the A2780(cisR) cell line as compared to that in A2780 cell line. Synergism was observed when Cis and Andro were administered using the sequences 0/4 h and 4/0 h. The percentage of apoptotic cell death was found to be greater for the 0/4 h combination of Andro and Cis as compared to those values from single-drug treatments. The results may be clinically significant if confirmed in vivo.

[682]

**TÍTULO / TITLE:** - DNA Methylation profiles as predictors of recurrence in non muscle invasive bladder cancer: an MS-MLPA approach.

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

**REVISTA / JOURNAL:** - J Exp Clin Cancer Res. 2013 Nov 19;32(1):94.

●● Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-94](#)

**AUTORES / AUTHORS:** - Casadio V; Molinari C; Calistri D; Tebaldi M; Gunelli R; Serra L; Falcini F; Zingaretti C; Silvestrini R; Amadori D; Zoli W

**RESUMEN / SUMMARY:** - BACKGROUND: Although non muscle invasive bladder cancer (NMIBC) generally has a good long-term prognosis, up to 80% of patients will nevertheless experience local recurrence after the primary tumor resection. The search for markers capable of accurately identifying patients at high risk of recurrence is ongoing. We retrospectively evaluated the methylation status of a panel of 23 tumor suppressor genes (TIMP3, APC, CDKN2A, MLH1, ATM, RARB, CDKN2B, HIC1, CHFR, BRCA1, CASP8, CDKN1B, PTEN, BRCA2, CD44, RASSF1, DAPK1, VHL, ESR1, TP73, IGSF4, GSTP1 and CDH13) in primary lesions to obtain information about their role in predicting local recurrence in NMIBC. METHODS: Formaldehyde-fixed paraffin-embedded (FFPE) samples from 74 patients operated on for bladder cancer were analyzed by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA): 36 patients had relapsed and 38 were disease-free at the 5-year follow up. Methylation status was considered as a dichotomous variable and genes showing methylation  $\geq 20\%$  were defined as "positive". RESULTS: Methylation frequencies were higher in non recurring than recurring tumors. A statistically significant difference was observed for HIC1 ( $P = 0.03$ ), GSTP1 ( $P = 0.02$ ) and RASSF1 ( $P = 0.03$ ). The combination of the three genes showed 78% sensitivity and 66% specificity in identifying recurrent patients, with an overall accuracy of 72%. CONCLUSIONS: Our preliminary data suggest a potential role of HIC1, GSTP1 and RASSF1 in predicting local recurrence in NMIBC. Such information could help clinicians to identify patients at high risk of recurrence who require close monitoring during follow up.

[683]

**TÍTULO / TITLE:** - Modulation of Mcl-1 sensitizes glioblastoma to TRAIL-induced apoptosis.

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

**REVISTA / JOURNAL:** - Apoptosis. 2013 Nov 9.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0935-2](#)

**AUTORES / AUTHORS:** - Murphy AC; Weyhenmeyer B; Noonan J; Kilbride SM; Schimansky S; Loh KP; Kogel D; Letai AG; Prehn JH; Murphy BM

**INSTITUCIÓN / INSTITUTION:** - Centre for Systems Medicine, Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, York House, St. Stephen's Green, Dublin, 2, Ireland.

**RESUMEN / SUMMARY:** - Glioblastoma (GBM) is the most aggressive form of primary brain tumour, with dismal patient outcome. Treatment failure is associated with intrinsic or acquired apoptosis resistance and the presence of a highly tumourigenic subpopulation of cancer cells called GBM stem cells. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) has emerged as a promising novel therapy for some

treatment-resistant tumours but unfortunately GBM can be completely resistant to TRAIL monotherapy. In this study, we identified Mcl-1, an anti-apoptotic Bcl-2 family member, as a critical player involved in determining the sensitivity of GBM to TRAIL-induced apoptosis. Effective targeting of Mcl-1 in TRAIL resistant GBM cells, either by gene silencing technology or by treatment with R-roscovitine, a cyclin-dependent kinase inhibitor that targets Mcl-1, was demonstrated to augment sensitivity to TRAIL, both within GBM cells grown as monolayers and in a 3D tumour model. Finally, we highlight that two separate pathways are activated during the apoptotic death of GBM cells treated with a combination of TRAIL and R-roscovitine, one which leads to caspase-8 and caspase-3 activation and a second pathway, involving a Mcl-1:Noxa axis. In conclusion, our study demonstrates that R-roscovitine in combination with TRAIL presents a promising novel strategy to trigger cell death pathways in glioblastoma.

[684]

**TÍTULO / TITLE:** - Addition of amino acid moieties to lapatinib increases the anti-cancer effect via amino acid transporters.

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

**REVISTA / JOURNAL:** - Biopharm Drug Dispos. 2013 Oct 22. doi: 10.1002/bdd.1872.

●● Enlace al texto completo (gratis o de pago) [1002/bdd.1872](#)

**AUTORES / AUTHORS:** - Maeng HJ; Kim ES; Chough C; Joung M; Lim JW; Shim CK; Shim WS

**INSTITUCIÓN / INSTITUTION:** - College of Pharmacy, Inje University, 607 Obang-dong, Gimhae, Gyeongnam, South Korea.

**RESUMEN / SUMMARY:** - Anti-cancer agents delivered to cancer cells often show multi-drug resistance (MDR) due to expulsion of the agents. One way to address this problem is to increase the accumulation of anti-cancer agents in cells via amino acid transporters. Thus, val-lapatinib and tyr-lapatinib were newly synthesized by adding valine and tyrosine moieties, respectively, to the parent anti-cancer agent lapatinib without stability issues in rat plasma. Val-lapatinib and tyr-lapatinib showed enhanced anti-cancer effects versus the parent lapatinib in various cancer cell lines, including human breast cancer cells (MDA-MB-231, MCF7) and lung cancer cells (A549), but not in non-cancerous MDCK-II cells. A glutamine uptake study revealed that both val-lapatinib and tyr-lapatinib, but not the parent lapatinib, inhibited glutamine transport in MDA-MB-231 and MCF7 cells, suggesting the involvement of amino acid transporters. In conclusion, val-lapatinib and tyr-lapatinib have enhanced anti-cancer effects, likely due to an increased uptake of the agents into cancer cells via amino acid transporters. The present data suggest that amino acid transporters may be an effective drug delivery target to increase the uptake of anti-cancer agents, leading to one method of overcoming MDR in cancer cells. Copyright © 2013 John Wiley & Sons, Ltd.

[685]

**TÍTULO / TITLE:** - Design, Synthesis and in Vitro Evaluation of 18beta-Glycyrrhetic Acid Derivatives for Anticancer Activity Against Human Breast Cancer Cell Line MCF-7.

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

**REVISTA / JOURNAL:** - Curr Med Chem. 2013 Nov 1.

**AUTORES / AUTHORS:** - Yadav DK; Kalani K; Singh AK; Khan F; Srivastava SK; Pant AB

**INSTITUCIÓN / INSTITUTION:** - Metabolic & Structural Biology Department, CSIR-Central Institute of Medicinal and Aromatic Plants, P.O.-CIMAP, Kukrail Picnic Spot Road, Lucknow-226015 (U.P.) India. [f.khan@cimap.res.in](mailto:f.khan@cimap.res.in).

**RESUMEN / SUMMARY:** - In the present work, QSAR model was derived by multiple linear regression method for the prediction of anticancer activity of 18beta-glycyrrhetic acid derivatives against the human breast cancer cell line MCF-7. The QSAR model for anti-proliferative activity against MCF-7 showed high correlation ( $r^2=0.89$  and  $r_{CV}^2=0.85$ ) and indicates that chemical descriptors namely, dipole moment (debye), steric energy (kcal/mole), heat of formation (kcal/mole), ionization potential (eV), LogP, LUMO energy (eV) and shape index (basic kappa, order 3) correlate well with activity. The QSAR predicted virtually active derivatives were first semi-synthesized and characterized on the basis of their  $^1H$  and  $^{13}C$  NMR spectroscopic data and then were in-vitro tested against MCF-7 cancer cell line. In particular, derivative of glycyrrhetic acid GA-12 has marked cytotoxic activity against MCF-7 similar to that of standard anticancer drug paclitaxel. The biological assays of active derivative selected by virtual screening showed significant experimental activity.

[686]

**TÍTULO / TITLE:** - The osteoprotegerin/tumor necrosis factor related apoptosis-inducing ligand axis in the kidney.

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

**REVISTA / JOURNAL:** - Curr Opin Nephrol Hypertens. 2013 Nov 16.

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

[1097/01.mnh.0000437611.42417.7a](https://doi.org/10.1007/01.mnh.0000437611.42417.7a)

**AUTORES / AUTHORS:** - Candido R

**INSTITUCIÓN / INSTITUTION:** - Diabetes Centre, A.S.S. 1 Triestina, Trieste, Italy.

**RESUMEN / SUMMARY:** - PURPOSE OF REVIEW: Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a cytokine belonging to the TNF superfamily. TRAIL may modulate cell survival and proliferation through interaction with two different receptors, TRAIL-R1 and TRAIL-R2. The actions of TRAIL are regulated by three decoy receptors, TRAIL-R3, TRAIL-R4 and osteoprotegerin (OPG). There is evidence that both TRAIL and OPG are expressed by renal cells. The OPG/TRAIL axis has been recently linked to the pathogenesis of renal damage and, in particular, diabetic nephropathy. RECENT FINDINGS: In patients with kidney diseases, serum TRAIL and OPG levels are increased in parallel and are significantly associated with each other. In diabetic nephropathy, the renal expression of TRAIL and OPG is elevated, and in tubular cells proinflammatory cytokines enhance TRAIL expression. Additionally, a high-glucose microenvironment sensitizes tubular cells to apoptosis induced by TRAIL, whereas OPG counteracts the actions of TRAIL in cultured cells. SUMMARY: It seems that the expression and levels of TRAIL and OPG at serum and kidney levels are crucial for the pathogenesis of kidney diseases, and in particular diabetic nephropathy. Although further studies are necessary to clarify the exact role of the OPG/TRAIL axis in the kidney, this system seems to hold promise to provide therapeutic approaches for the management of renal damage. VIDEO ABSTRACT

AVAILABLE: See the Video Supplementary Digital Content 1  
(<http://links.lww.com/CONH/A5>).

[687]

**TÍTULO / TITLE:** - Pro-apoptotic activity of new analog of anthracyclines - WP 631 in advanced ovarian cancer cell line.

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

**REVISTA / JOURNAL:** - Toxicol In Vitro. 2013 Nov 25. pii: S0887-2333(13)00310-X. doi: 10.1016/j.tiv.2013.11.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.11.006](http://1016/j.tiv.2013.11.006)

**AUTORES / AUTHORS:** - Gajek A; Denel M; Bukowska B; Rogalska A; Marczak A

**INSTITUCIÓN / INSTITUTION:** - Department of Thermobiology, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143, 90-236 Lodz, Poland. Electronic address: [arekgajek86@wp.pl](mailto:arekgajek86@wp.pl).

**RESUMEN / SUMMARY:** - In this work we investigated the mode of cell death induced by WP 631, a novel anthracycline antibiotic, in the ovarian cancer cell line (OV-90) derived from the malignant ascites of a patient diagnosed with advanced disease. The effects were compared with those of doxorubicin (DOX), a first generation anthracycline. The ability of WP 631 to induce apoptosis and necrosis was examined by double staining with Annexin V and propidium iodide, measurements of the level of intracellular calcium ions and cytochrome c, PARP cleavage. We also investigated the possible involvement of the caspases activation, DNA degradation (comet assay) and intracellular reactive oxygen species (ROS) production in the development of the apoptotic events and their significance for drug efficiency. The results obtained clearly demonstrate that antiproliferative capacity of WP 631 in tested cell line was a few times greater than that of DOX. Furthermore, ovarian cancer cells treated with WP 631 showed a higher mean level of basal DNA damage in comparison to DOX. In conclusion, WP 631 is able to induce caspase - dependent apoptosis in human ovarian cancer cells. Obtained results suggested that WP 631 may be a candidate for further evaluation as chemotherapeutic agents for human cancers.

[688]

**TÍTULO / TITLE:** - Bone marrow leukaemic transformation of myelodysplastic syndrome revealed by a cutaneous Langerhans cell infiltrate: partial response to azacitidine.

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

**REVISTA / JOURNAL:** - Eur J Dermatol. 2013 Oct 1;23(5):710-1. doi: 10.1684/ejd.2013.2132.

●● Enlace al texto completo (gratis o de pago) [1684/ejd.2013.2132](http://1684/ejd.2013.2132)

**AUTORES / AUTHORS:** - Osio A; Elfatoiki F; Raffoux E; Vignon-Pennamen MD; de Labarthe A; Cordoliani F; Petrella T; Bagot M; Janin A; Battistella M; Bouaziz JD

**INSTITUCIÓN / INSTITUTION:** - Universite Paris Diderot, Laboratoire de Pathologie, UMR-S 728, Paris, France, INSERM U728, city>Paris, France, Laboratoire de Pathologie.

[689]

**TÍTULO / TITLE:** - A Randomized Study of Interferon alpha-2b Versus No Treatment as Consolidation After High Dose Therapy and Autologous Stem Cell Transplantation for Patients With Relapsed Lymphoma.

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

**REVISTA / JOURNAL:** - Oncologist. 2013;18(11):1189. doi: 10.1634/theoncologist.2013-0223. Epub 2013 Oct 8.

●● Enlace al texto completo (gratis o de pago) [1634/theoncologist.2013-0223](#)

**AUTORES / AUTHORS:** - Bosly A; Grigg A; Holte H; Gisselbrecht C; Radford J; Rossi A; Lopez-Guillermo A; Trneny M; Sebban C; Hagberg H; Leal da Costa F; Colombat P; Bron D; Coiffier B

**INSTITUCIÓN / INSTITUTION:** - CHU UCL Mont-Godinne-Dinant, Yvoir, Belgium;

**RESUMEN / SUMMARY:** - Patients with lymphoma who have experienced a first relapse or progression and have disease deemed sensitive to salvage chemotherapy nevertheless have a high likelihood of having a second relapse. To decrease the likelihood of a second relapse after high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), interferon (IFN) alpha-2b was given in a prospective randomized international trial. Methods. In this trial, 221 patients with varying histologic diagnoses (8 small lymphocytic, 37 follicular, 9 mantle, 90 diffuse large B-cell, 20 peripheral T-cell, 3 high-grade B-cell non-Hodgkin lymphoma, and 54 Hodgkin lymphoma) were randomly assigned to receive no further treatment (arm A: 117 patients) or IFNalpha-2b, 3 MU three times weekly, for 18 months (arm B: 104 patients). Results. In arm B, 21 patients (20%) did not receive IFNalpha-2b because of early progression or absence of hematologic recovery, 29 patients (28%) completed the 18 months of treatment, and 54 patients (52%) interrupted treatment because of progression (23%) or toxicity (29%). Event-free survival and overall survival were not different between the two arms on an intent-to-treat analysis and also if analysis was restricted to patients who were alive and had not experienced disease progression three months after transplantation. The study was not sufficiently powered to evaluate effects in histologic subtypes. Conclusion. In this trial, post-autograft IFNalpha-2b did not improve outcomes in a heterogeneous group of patients with lymphoma.

[690]

**TÍTULO / TITLE:** - Challenging single- and multi-probesets gene expression signatures of pathological complete response to neoadjuvant chemotherapy in breast cancer: Experience of the REMAGUS 02 phase II trial.

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

**REVISTA / JOURNAL:** - Breast. 2013 Dec;22(6):1052-9. doi: 10.1016/j.breast.2013.08.015. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1016/j.breast.2013.08.015](#)

**AUTORES / AUTHORS:** - Valet F; de Cremoux P; Spyrtatos F; Servant N; Dujaric ME; Gentien D; Lehmann-Che J; Scott V; Sigal-Zafrani B; Mathieu MC; Bertheau P; Guinebretiere JM; Pierga JY; Delaloge S; Giacchetti S; Brain E; Tembo O; Marty M; Asselain B

**INSTITUCIÓN / INSTITUTION:** - Department of Biostatistics, Curie Institute, Paris 75248, France; Inserm U900, Curie Institute, Paris 75248, France.

**RESUMEN / SUMMARY:** - This study was designed to identify predictive signatures of pathological complete response (pCR) in breast cancer treated by taxane-based

regimen, using clinicopathological variables and transcriptomic data (Affymetrix Hgu133 Plus 2.0 devices). The REMAGUS 02 trial (n = 153, training set) and the publicly available M.D. Anderson data set (n = 133, validation set) were used. A re-sampling method was applied. All predictive models were defined using logistic regression and their classification performances were tested through Area Under the Curve (AUC) estimation. A stable set of 42 probesets (31 genes) differentiate pCR or no pCR samples. Single-or 2-probesets signatures, mainly related to ER pathway, were equally predictive of pCR with AUC greater than 0.80. Models including probesets associated with ESR1, MAPT, CA12 or PIGH presented good classification performances. When clinical variables were entered into the model, only CA12 and PIGH, remained informative (p = 0.05 and p = 0.005) showing that a combination of a few genes provided robust and reliable prediction of pCR.

[691]

**TÍTULO / TITLE:** - Study of Antitumor Activity of Antibodies to TNF-alpha on Walker Carcinoma Model.

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

**REVISTA / JOURNAL:** - Bull Exp Biol Med. 2013 Aug;155(5):673-5.

**AUTORES / AUTHORS:** - Yurlova EI; Krylova SG; Dugina JL; Epstein OI

**INSTITUCIÓN / INSTITUTION:** - Institute of Pharmacology, Siberian Division of the Russian Academy of Medical Sciences, Tomsk; Materia Medica Holding, Moscow, Russia. [JurlovaEI@materiamedica.ru](mailto:JurlovaEI@materiamedica.ru).

**RESUMEN / SUMMARY:** - The effect of release-active antibodies to TNF-alpha (Arthrofon) on the development of Walker carcinoma 256 was studied in Wistar rats. Intragastric dose of this drug significantly inhibited the growth of tumor node (55% inhibition of tumor growth), but less effectively than the reference drug cyclophosphamide (80%). The studied drug significantly prolonged animal' lifespan (+97%) and its efficiency in this respect was comparable to that of cyclophosphamide (+96%).

[692]

**TÍTULO / TITLE:** - Therapeutic proteins in tumors and targeted therapeutic agents for cancer patients.

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

**REVISTA / JOURNAL:** - Protein Pept Lett. 2013 Dec;20(12):1345-59.

**AUTORES / AUTHORS:** - Kesikli SA; Kilickap S

**INSTITUCIÓN / INSTITUTION:** - Hacettepe University Cancer Institute, Department of Preventive Oncology, 06100 Altindag, Ankara, Turkey. [skilickap@yahoo.com](mailto:skilickap@yahoo.com).

**RESUMEN / SUMMARY:** - The identification of novel molecular targets has paved the way for new treatment options in cancer patients. A number of agents targeting molecules that are crucial both for the tumor and its microenvironment have already been approved by the U.S. Food and Drug Administration for clinical use. The monoclonal antibodies and the small molecule kinase inhibitors constitute two major classes of targeted therapeutic agents, which have apparently different mechanisms of action, toxicity profiles, routes of administration, timing and dosing. Moreover, individual differences in genes regulating the distribution and metabolism of targeted agents

evidently influence treatment outcomes. Data regarding the immune- and tumor microenvironment-modulatory properties of most of these agents are either obscure or controversial, as well. Therefore, preclinical animal and human studies that aim to identify the immunological, biological and the pharmacological properties of these novel classes of agents that also employ recent developments in pharmacogenomics and proteomics are warranted.

[693]

**TÍTULO / TITLE:** - Impact of cytotoxic and targeted antineoplastic drugs on the validity of the mitogen-induced interferon-gamma release assay for latent tuberculosis infection: Results of a prospective trial at a comprehensive cancer center.

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

**REVISTA / JOURNAL:** - Scand J Infect Dis. 2013 Oct 10.

●● Enlace al texto completo (gratis o de pago) [3109/00365548.2013.840919](#)

**AUTORES / AUTHORS:** - Rodriguez GH; Safdar A

**INSTITUCIÓN / INSTITUTION:** - From the The University of Texas MD Anderson Cancer Center, Houston, Texas.

**RESUMEN / SUMMARY:** - The T-SPOT.TB test (TS.TB), an interferon-gamma (IFN-gamma) release assay (IGRA), is superior in diagnosing latent tuberculosis infection compared with the conventional tuberculin skin test (TST). However, whether cytotoxic chemotherapy and treatment with new-generation antineoplastic monoclonal antibodies affects the TS.TB is not certain. We evaluated the feasibility of using the TS.TB in this population. Sixteen cancer patients at high risk for tuberculosis exposure were prospectively evaluated with the TST and TS.TB. Blood samples were obtained 7.5 +/- 89.3 days after the most recent cycle of antineoplastic therapy. Six patients (38%) were febrile within 24 h of blood sampling; high-dose corticosteroid therapy and profound treatment-induced neutropenia were present in 1 patient each. In all patients, TS.TB showed no evidence of latent tuberculosis infection. A robust mitogen-induced IFN-gamma response was seen in samples from 14 patients (88%) despite therapy with high-dose corticosteroids, cyclophosphamide, fludarabine, gemtuzumab, ozogamicin, and alemtuzumab. The presence of fever or profound neutropenia did not negatively impact mitogen response by peripheral lymphocytes. The 2 patients whose peripheral blood lymphocytes (> 500 cells/ml) failed to generate a cytokine response to ex vivo mitogen stimulation had refractory advanced cancer. Unlike the TST, a negative TS.TB provided interpretable results even in cancer patients undergoing new-generation immunosuppressive therapy.

[694]

**TÍTULO / TITLE:** - XPD gene polymorphisms and the effects of induction chemotherapy in cytogenetically normal de novo acute myeloid leukemia patients.

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

**REVISTA / JOURNAL:** - Hematology. 2013 Nov 27.

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

[1179/1607845413Y.0000000144](#)

**AUTORES / AUTHORS:** - El-Tokhy MA; Hussein NA; Bedewy AM; Barakat MR

**RESUMEN / SUMMARY:** - BACKGROUND: Cytogenetically normal acute myeloid leukemia (AML) represents nearly half of newly diagnosed de novo AML cases. XPD is one of the DNA repair proteins, whose genetic polymorphisms are thought to affect their function as regards response to chemotherapeutic drugs and chemotherapy-induced toxicities. SUBJECTS AND METHODS: We investigated the XPD Asp312Asn and Lys751Gln polymorphisms by polymerase chain reaction-restriction fragment length polymorphism in 51 newly diagnosed cytogenetically normal de novo AML patients. The response to the standard induction chemotherapy protocol and chemotherapy-induced toxicities were monitored. RESULTS: The XPD Asp312Asn GG genotype was the most frequent (57%) followed by the GA variant (37%), and the AA variant was the least frequent (6%). As regards the XPD Lys751Gln polymorphism, the AA genotype was the most frequent (49%), followed by the AC (39%) and CC (12%) variants. These variants were not associated with age, sex, FAB subtype, CNS infiltration, chemotherapy-induced hepatotoxicity, nephrotoxicity, or metabolic toxicity. The XPD Lys751Gln CC polymorphic variant was associated with chemotherapy-induced cardiotoxicity and lower chance to achieve response to induction chemotherapy. CONCLUSION: XPD Lys751Gln and not Asp312Asn polymorphism was associated with chemotherapy-induced cardiotoxicity and response to induction chemotherapy in newly diagnosed cytogenetically normal AML patients. Pretreatment assay of XPD Lys751Gln may help to anticipate cardiotoxicity in those at risk. Moreover, it may be considered a prognostic marker in AML cases. However, further large scale research is needed to verify its usefulness.

[695]

**TÍTULO / TITLE:** - The presence and prognostic impact of apoptotic and nonapoptotic disseminated tumor cells in the bone marrow of primary breast cancer patients after neoadjuvant chemotherapy.

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

**REVISTA / JOURNAL:** - Breast Cancer Res. 2013 Oct 8;15(5):R94.

●● [Enlace al texto completo \(gratis o de pago\) 1186/bcr3496](#)

**AUTORES / AUTHORS:** - Hartkopf AD; Taran FA; Wallwiener M; Hagenbeck C; Melcher C; Krawczyk N; Hahn M; Wallwiener D; Fehm T

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, University of Tuebingen, Calwer Strasse 7, 72076 Tuebingen, Germany.

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**RESUMEN / SUMMARY:** - INTRODUCTION: Neoadjuvant systemic therapy of primary breast cancer (PBC) patients offers the possibility to monitor treatment response. However, patients might have metastatic relapse despite achieving a pathologic complete response (pCR). This indicates that local response to therapy must not be representative for systemic treatment efficacy. Therefore, the aim of this study was to compare local response with systemic tumor cell dissemination by determining the presence of disseminated tumor cells (DTCs), including apoptotic tumor cells, in the bone marrow (BM) of PBC patients after neoadjuvant chemotherapy (NACT). METHODS: DTCs were detected by immunocytochemistry (pancytokeratin antibody A45-B/B3) and cytomorphology (DTC status). The presence of apoptotic tumor cells was determined by using the M30 antibody (M30 status). This antibody detects a neo-epitope that is expressed only during early apoptosis. RESULTS: BM aspirates from

400 PBC patients that had completed NACT were eligible for this study. Of these, 167 (42%) patients were DTC positive (DTC status). The M30 status was investigated in 308 patients. Apoptotic (M30-positive) tumor cells were detected in 89 (29%) of these. Whereas the DTC status was not correlated ( $P = 0.557$ ) to local treatment response (that is, pCR or a clinical complete/partial response), the presence of M30-positive tumor cells was significantly higher in patients that responded to therapy ( $P = 0.026$ ). Additionally, DTC-positive patients were at an increased risk for disease relapse (hazard ratio, 1.87; 95% CI, 1.11 to 3.15;  $P = 0.019$ ). CONCLUSION: The presence of DTC is independent of therapy response of the primary tumor. As patients that are DTC positive after NACT have an unfavorable outcome, they might benefit from additional systemic treatment.

[696]

**TÍTULO / TITLE:** - Prognostic impact of Wilms tumor gene mutations in Egyptian patients with acute myeloid leukemia with normal karyotype.

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

**REVISTA / JOURNAL:** - Hematology. 2013 Sep 26.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1179/1607845413Y.0000000129](#)

**AUTORES / AUTHORS:** - Zidan MA; Shaaban HM; Elghannam DM

**RESUMEN / SUMMARY:** - The Wilms' tumor (WT1) gene mutations were detected in patients with most forms of acute leukemia. However, the biological significance and the prognostic impact of WT1 mutation in Egyptian patients with acute myeloid leukemia with normal karyotype (AML-NK) are still uncertain. We aimed to evaluate the incidence and clinical relevance of WT1 gene mutations in acute myeloid leukemia with normal karyotype (AML-NK). Exons 7 and 9 of WT1 were screened in samples from 216 adult NK-AML using polymerase chain reaction single-strand conformation polymorphism techniques. Twenty-three patients (10.6%) harbored WT1 mutations. Younger ages and higher marrow blasts were significantly associated with WT1 mutations ( $P = 0.006$  and  $0.003$  respectively). Complete remission rates were significantly lower in patients with WT1 mutations than those with WT1 wild-type ( $P = 0.015$ ). Resistance, relapse, and mortality rates were significantly higher in patients with WT1 mutations than those without ( $P = 0.041$ ,  $0.016$ , and  $0.008$  respectively). WT1 mutations were inversely associated with NPM1 mutations ( $P = 0.007$ ). Patients with WT1 mutations had worse disease-free survival ( $P < 0.001$ ) and overall survival ( $P < 0.001$ ) than patients with WT1 wild-type. In multivariable analyses, WT1 mutations independently predicted worse DFS ( $P < 0.001$ ; hazard ratio [HR] 0.036) and overall survival ( $P = 0.001$ ; HR = 0.376) when controlling for age, total leukocytic count (TLC), and NPM1 mutational status. In conclusion, WT1 mutations are a negative prognostic indicator in intensively treated patients with AML-NK, may be a part of molecularly based risk assessment and risk-adapted treatment stratification of patients with AML-NK.

[697]

**TÍTULO / TITLE:** - High-Dose Etoposide Plus Granulocyte Colony-Stimulating Factor as an Effective Chemomobilization Regimen for Autologous Stem Cell Transplantation in

Patients with Non-Hodgkin Lymphoma Previously Treated with CHOP-based Chemotherapy: A Study from the Consortium for Improving Survival of Lymphoma.

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

**REVISTA / JOURNAL:** - Biol Blood Marrow Transplant. 2013 Oct 17. pii: S1083-8791(13)00460-6. doi: 10.1016/j.bbmt.2013.10.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbmt.2013.10.012](#)

**AUTORES / AUTHORS:** - Hyun SY; Cheong JW; Kim SJ; Min YH; Yang DH; Ahn JS; Lee WS; Ryou HM; Do YR; Lee HS; Lee JH; Oh SY; Suh C; Yhim HY; Kim JS

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

**RESUMEN / SUMMARY:** - We conducted a multicenter retrospective study to compare the efficacy and toxicity of various chemomobilization regimens: high-dose (HD) cyclophosphamide, HD etoposide (VP-16), and platinum-based chemotherapies. We reviewed the experiences of 10 institutions with 103 non-Hodgkin lymphoma patients who had previously only been treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy. The mobilization yields for each regimen were analyzed. HD VP-16 mobilized a significantly higher median number of CD34+ cells (16.22 x 10<sup>6</sup> cells/kg) than HD cyclophosphamide (4.44 x 10<sup>6</sup> cells/kg) or platinum-based chemotherapies (6.08 x 10<sup>6</sup> cells/kg, P < .001). The rate of successful mobilization (CD34+ cell count  $\geq$ 5.0 x 10<sup>6</sup> cells/kg) was also significantly higher for HD VP-16 (86%) than for HD cyclophosphamide (45%) or platinum-based chemotherapies (61%, P = .004). The successful mobilization rate on day 1 of 72% for HD VP-16 was significantly higher than the rates for HD cyclophosphamide (13%) and platinum-based chemotherapies (26%, P < .001). In multivariate analysis, HD VP-16 was a significant predictor of successful mobilization (P = .014; odds ratio, 5.25; 95% confidence interval, 1.40 to 19.63). Neutropenic fever occurred in 67% of patients treated with HD VP-16. The incidence was similar for HD cyclophosphamide (58%, P = .454) but was significantly lower for platinum-based chemotherapies (12%, P < .001). However, fatal (grade  $\geq$  4) infection and treatment-related mortality were not observed in this study. In conclusion, the mobilization yield was significantly influenced by the chemomobilization regimen, and HD VP-16 was a highly effective mobilization regimen in patients with non-Hodgkin lymphoma.

[698]

**TÍTULO / TITLE:** - MIB-1 labeling index as a prognostic factor for patients with follicular lymphoma treated with rituximab plus CHOP therapy.

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

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Sep 21. doi: 10.1111/cas.12288.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12288](#)

**AUTORES / AUTHORS:** - Yamamoto E; Tomita N; Sakata S; Tsuyama N; Takeuchi K; Nakajima Y; Miyashita K; Tachibana T; Takasaki H; Tanaka M; Hashimoto C; Koharazawa H; Fujimaki K; Taguchi J; Harano H; Motomura S; Ishigatsubo Y

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan.

**RESUMEN / SUMMARY:** - The MIB-1 labeling index, which is based on Ki67 immunostaining, is widely used to evaluate the proliferation of tumor cells in lymphoma.

However, its clinical significance has not been fully assessed. We retrospectively evaluated the prognostic impact of the MIB-1 labeling index at the time of diagnosis, in 98 patients with follicular lymphoma (FL) grade 1-3b who were treated uniformly with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy. The 5-year progression-free survival (PFS) for an MIB-1 labeling index of  $\geq 10\%$  (n = 60) and  $< 10\%$  (n = 38) was 35% and 61%, respectively (P = 0.015). The 5-year overall survival (OS) for an MIB-1 labeling index of  $\geq 10\%$  and  $< 10\%$  was 77% and 92%, respectively (P = 0.025). Pathological grading was not correlated with PFS or OS. In multivariate analysis, an MIB-1 labeling index of  $\geq 10\%$  was independently associated with poor PFS and OS. In conclusion, an MIB-1 labeling index of 10% is a useful cut-off level for predicting the prognosis of patients with FL.

[699]

**TÍTULO / TITLE:** - Phase II Trial of Fulvestrant With Metronomic Capecitabine for Postmenopausal Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer.

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

**REVISTA / JOURNAL:** - Clin Breast Cancer. 2013 Sep 27. pii: S1526-8209(13)00216-4. doi: 10.1016/j.clbc.2013.09.003.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.clbc.2013.09.003](#)

**AUTORES / AUTHORS:** - Schwartzberg LS; Wang G; Somer BG; Blakely LJ; Wheeler BM; Walker MS; Stepanski EJ; Houts AC

**INSTITUCIÓN / INSTITUTION:** - The West Clinic, Memphis, TN. Electronic address: [lschwartzberg@westclinic.com](mailto:lschwartzberg@westclinic.com).

**RESUMEN / SUMMARY:** - BACKGROUND: In this phase II study, we explored efficacy and toxicity of combined endocrine and low-dose metronomic chemotherapy therapy consisting of fulvestrant and capecitabine in estrogen and/or progesterone receptor-positive, HER2-negative MBC. PATIENTS AND METHODS: Patients with  $\leq 1$  previous hormonal treatment in the metastatic setting received an injection fulvestrant loading dose 500 mg on day 1, 250 mg on days 15 and 29 followed by 250 mg every 28 days along with continuous oral capecitabine in divided doses. The total fixed daily dose of capecitabine was either 1500 mg or 2000 mg, depending on the patient's weight ( $< 80$  kg vs.  $\geq 80$  kg). Primary end points were PFS and TTP. Toxicity was assessed by continuous evaluations of treatment-emergent adverse events (AEs) and changes from baseline in laboratory values. RESULTS: Forty-one women, with a mean age of 64.5 years, were enrolled. Patients completed a median of 11 monthly treatment cycles. Median PFS was 14.98 months (95% confidence interval [CI], 7.26-upper limit [UL] not estimated) and median TTP was 26.94 months (95% CI, 7.26-UL not estimated). Median overall survival was 28.65 months (95% CI, 23.95-UL not estimated). Treatment was well tolerated with  $< 10\%$  Grade 3 palmar-plantar erythrodysesthesia. Overall, the most frequent AEs were palmar-plantar erythrodysesthesia, fatigue, and nausea. CONCLUSION: Fulvestrant with metronomic capecitabine demonstrates substantial activity in hormone receptor-positive MBC and is well tolerated. Combined chemoendocrine approaches should be further explored considering the low toxicity of the combination with meaningful TTP.

[700]

**TÍTULO / TITLE:** - Treatment effect of capecitabine and docetaxel or docetaxel alone by oestrogen receptor status in patients with metastatic breast cancer: Results of an exploratory analysis.

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

**REVISTA / JOURNAL:** - Breast. 2013 Dec;22(6):1087-93. doi: 10.1016/j.breast.2013.08.016. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1016/j.breast.2013.08.016](#)

**AUTORES / AUTHORS:** - Gluck S; Russell C; O'Shaughnessy J; McKenna EF; Hu S; Odom D; Blum JL

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Division of Hematology/Oncology, University of Miami, Leonard M Miller School of Medicine, Sylvester Comprehensive Cancer Center, 1475 NW 12<sup>th</sup> Avenue, Miami, FL 33136, USA. Electronic address: [SGluck@med.miami.edu](mailto:SGluck@med.miami.edu).

**RESUMEN / SUMMARY:** - We investigated treatment effects by oestrogen receptor (ER) status among women with metastatic breast cancer (MBC) receiving capecitabine © plus docetaxel (D) or D alone in a randomised phase III trial. Data were retrospectively analysed from patients whose disease had recurred following (neo)adjuvant anthracyclines. ER status was identified in 356/506 patients. In patients with ER-positive tumours, median overall survival from enrolment was 17.7 months with CD versus 12.5 months with D (hazard ratio [HR] 0.65, 95% confidence interval [CI]: 0.47-0.89; P = 0.007) and median time to progression (TTP) was 6.8 and 5.4 months, respectively (HR 0.62, 95% CI: 0.46-0.84; P = 0.002). For patients with ER-negative tumours, significantly longer TTP was seen with CD (5.2 versus 3.5 months; HR 0.73, 95% CI: 0.53-0.98; P = 0.038). Whether there is an additional C to D treatment benefit in ER-positive versus ER-negative MBC requires further evaluation.

[701]

**TÍTULO / TITLE:** - p53 accumulation is a strong predictor of recurrence in estrogen receptor-positive breast cancer patients treated with aromatase inhibitors.

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

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Oct 10. doi: 10.1111/cas.12302.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12302](#)

**AUTORES / AUTHORS:** - Yamamoto M; Hosoda M; Nakano K; Jia S; Hatanaka KC; Takakuwa E; Hatanaka Y; Matsuno Y; Yamashita H

**INSTITUCIÓN / INSTITUTION:** - Breast and Endocrine Surgery, Hokkaido University Hospital, Sapporo, Japan.

**RESUMEN / SUMMARY:** - Aromatase inhibitors have played a central role in endocrine therapy for estrogen receptor (ER)-positive breast cancer in postmenopausal women. However, factors predictive of the efficacy of aromatase inhibitors, and prognostic factors, both for early and late recurrence in women treated with adjuvant aromatase inhibitors have not been identified. Whole genome analysis identified that a TP53 gene mutation exists in ER-positive breast cancers, although the frequency of TP53 gene mutation in luminal tumors is lower compared with basal-like or human epidermal growth factor receptor type 2 (HER2)-positive breast cancers. We examined expression of p53, as well as ER, progesterone receptor, HER2 and Ki-67 using immunohistochemistry in postmenopausal ER-positive breast cancer patients who

were treated with aromatase inhibitors as adjuvant endocrine therapy. There were 53 (21%) tumors that contained 10% or more p53-positive cells. High p53 expression was positively correlated with tumor grade, HER2 score and Ki-67 expression. Significant association was observed between disease-free survival and high p53 expression in multivariate analysis ( $P < 0.0001$ ). Compared with women without recurrence, women with early recurrence had significantly higher p53 expression ( $P < 0.0001$ ), as did women with late recurrence ( $P = 0.037$ ). The present study demonstrates that p53 accumulation is a strong predictor of both early and late recurrence in ER-positive breast cancer patients treated with aromatase inhibitors as adjuvant endocrine therapy. TP53 gene alteration might be a key biological characteristic of ER-positive breast cancer.

[702]

**TÍTULO / TITLE:** - Prediction of Poor Mobilization of Autologous CD34+ Cells with Growth Factor in Multiple Myeloma Patients: Implications for Risk-Stratification.

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

**REVISTA / JOURNAL:** - Biol Blood Marrow Transplant. 2013 Nov 6. pii: S1083-8791(13)00508-9. doi: 10.1016/j.bbmt.2013.11.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbmt.2013.11.003](http://1016/j.bbmt.2013.11.003)

**AUTORES / AUTHORS:** - Costa LJ; Nista EJ; Buadi FK; Lacy MQ; Dispenzieri A; Kramer CP; Edwards KH; Kang Y; Gertz MA; Stuart RK; Kumar S

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology and Oncology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina. Electronic address: [costalj@musc.edu](mailto:costalj@musc.edu).

**RESUMEN / SUMMARY:** - It is unknown whether clinical characteristics can successfully predict which multiple myeloma (MM) patients would be poor mobilizers with growth factor (GF) alone so they can be assigned to mobilization with chemotherapy + GF or GF + plerixafor. MM patients (N = 477) who underwent autologous mobilization with GF were retrospectively reviewed and assigned into training and validation cohorts. In multiple regression analysis, age, platelet count at time of mobilization, type of GF utilized, and extent of exposure to lenalidomide independently correlated with peripheral blood (PB)-CD34+ and were integrated in a predicting score (PS) for poor mobilizers, defined as PB-CD34+ < 20/mm<sup>3</sup> 4 days after initiation of GF. There was no correlation between institution, gender, time between diagnosis, and mobilization or plasma cells in the bone marrow at time of mobilization and PBCD34+. The PS cut-off found in the training cohort to have 90% sensitivity for prediction of poor mobilizers performed with 89.7% sensitivity but only 34.8% specificity in the validation cohort. Conversely, the PS cut-off developed to have 90% specificity performed with 86.9% specificity but only 37% sensitivity. We conclude that clinical characteristics identifiable before initiation of mobilization should not be used to stratify MM patients for different mobilization strategies.

[703]

**TÍTULO / TITLE:** - CpG island methylator phenotype and its relationship with prognosis in adult acute leukemia patients.

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

**REVISTA / JOURNAL:** - Hematology. 2013 Oct 25.

- Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000137](https://doi.org/10.1179/1607845413Y.0000000137)

**AUTORES / AUTHORS:** - Fu HY; Wu DS; Zhou HR; Shen JZ

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To investigate the relationship between CpG island methylator phenotype (CIMP) and prognosis in adults with acute leukemia. **METHODS:** Bone marrow samples from 53 acute myeloid leukemia and 50 acute lymphoblastic leukemia patients were collected. The methylation status of 18 tumor suppressor genes was determined using methylation-specific polymerase chain reaction. **RESULTS:** Greater than 30% of acute leukemia patients had methylated p15, p16, CDH1, CDH13, RUNX3, sFRP1, ID4, and DLC-1 genes; methylation of  $\geq 4$  were defined as CIMP positive. Age, type of leukemia, white blood cell count, and CIMP status were significantly associated with recurrence-free survival (RFS) and overall survival (OS) ( $P < 0.05$ ). CIMP status was an independent prognostic factor for OS (hazard ratio: 2.07, 95% confidence interval: 1.03-4.15,  $P = 0.040$ ). CIMP-negative patients had significantly improved RFS and OS ( $P < 0.05$ ). p16 and DLC1 methylation was significantly associated with RFS and OS ( $P < 0.05$ ). **CONCLUSIONS:** CIMP may serve as an independent risk factor for evaluating the prognosis of patients with acute leukemia.

[704]

**TÍTULO / TITLE:** - Single-dose infliximab in hepatitis C genotype 1-naive patients with high serum tumour necrosis factor- $\alpha$  does not influence efficacy of pegylated interferon  $\alpha$ -2b/ribavirin therapy.

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

**REVISTA / JOURNAL:** - Can J Gastroenterol. 2013 Nov 8. pii: 15887.

**AUTORES / AUTHORS:** - Cooper C; Shafran S; Greenbloom S; Enns R; Farley J; Hilzenrat N; Williams K; Elkashab M; Abadir N; Neuman M

[705]

**TÍTULO / TITLE:** - Interferon- $\gamma$  produced by tumor-infiltrating NK cells and CD4 T cells downregulates TNFSF15 expression in vascular endothelial cells.

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

**REVISTA / JOURNAL:** - Angiogenesis. 2013 Oct 20.

- Enlace al texto completo (gratis o de pago) [1007/s10456-013-9397-y](https://doi.org/10.1007/s10456-013-9397-y)

**AUTORES / AUTHORS:** - Lu Y; Gu X; Chen L; Yao Z; Song J; Niu X; Xiang R; Cheng T; Qin Z; Deng W; Li LY

**INSTITUCIÓN / INSTITUTION:** - College of Pharmacy, State Key Laboratory of Medicinal Chemical Biology and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin, China.

**RESUMEN / SUMMARY:** - Endothelial cells in an established vasculature secrete tumor necrosis factor superfamily-15 (TNFSF15; VEGI; TL1A) that functions as a negative modulator of neovascularization to maintain blood vessel stability. TNFSF15 gene expression diminishes at angiogenesis and inflammation sites such as in cancers and wounds. We reported previously that vascular endothelial growth factor and monocyte chemoattractant protein-1 contribute to TNFSF15 downmodulation in ovarian cancer. Here

we show that interferon-gamma (IFN $\gamma$ ) suppresses TNFSF15 expression in human umbilical vein endothelial cells. This activity is mediated by IFN $\gamma$  receptor and the transcription factor STAT1. Immunohistochemical analysis of ovarian cancer clinical specimens indicates that TNFSF15 expression diminishes while tumor vascularity increases in specimens with high-grades of IFN $\gamma$  expression. Since tumor-infiltrating NK and CD4+ T cells are the main sources of IFN $\gamma$  in tumor lesions, we isolated these cells from peripheral blood of healthy individuals, treated the cells with ovarian cancer OVCAR3 cell-conditioned media, and found a onefold and tenfold increase of IFN $\gamma$  production in NK and CD4+ T cells, respectively, compared with that in vehicle-treated cells. These findings support the view that tumor-infiltrating NK and CD4+ T cells under the influence of cancer cells significantly increase the production of IFN $\gamma$ , which in turn inhibits TNFSF15 expression in vascular endothelial cells, shifting the balance of pro- and anti-angiogenic factors toward escalated angiogenesis potential in the tumor.

[706]

**TÍTULO / TITLE:** - O-(2-[F]fluoroethyl)-L-tyrosine uptake is an independent prognostic determinant in patients with glioma referred for radiation therapy.

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

**REVISTA / JOURNAL:** - Ann Nucl Med. 2013 Nov 24.

●● Enlace al texto completo (gratis o de pago) [1007/s12149-013-0792-7](#)

**AUTORES / AUTHORS:** - Sweeney R; Polat B; Samnick S; Reiners C; Flentje M; Verburg FA

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, University of Wurzburg, Wurzburg, Germany.

**RESUMEN / SUMMARY:** - AIM: To evaluate the prognostic value of O-(2-[18F]fluoroethyl)-L-tyrosine positron emission tomography (FET-PET) uptake intensity in World Health Organisation (WHO) tumor grade II-IV gliomas. METHODS: We studied 28 patients with WHO tumor grade II-IV gliomas who were referred to our department for radiation therapy. We acquired a FET-PET in all patients, as well as magnetic resonance imaging (MRI) of the brain consisting of at least T2-weighted imaging, flair and pre- and post-contrast T1-weighted imaging. SUVmax was measured and the tumor-to-brain uptake ratio (TBR) of all lesions was calculated based on the SUVmax (TBRmax) or SUVmean (TBRmean) of the contralateral healthy tissue. For this study, volumes were calculated using MRI alone, MRI + the volume with a SUVmax on FET-PET  $\geq 2.2$  as well as MRI + the volume with an uptake of at least 40 % of the SUVmax. RESULTS: Tumor volumes were a median (range) of 88.6 (2.6-467.4) ml (MRI alone), 84.2 (2.8-474.4) ml (MRI + SUVmax on FET-PET  $\geq 2.2$ ) and 101.5 (4.0-512.1) ml (MRI + FET-PET uptake  $\geq 40$  % SUVmax), respectively. TBR-SUVmean was 2.36 (1.46-4.08); TBR-SUVmax was 1.71 (0.97-2.85). During a follow-up of 18.7 (2.5-36.1) months after FET-PET, 12 patients died of malignant glioma. Patients with a SUVmax  $\geq 2.6$  had a significantly worse tumor-related mortality ( $p = 0.005$ ) and progression-free survival ( $p = 0.038$ ) than those with a lower SUVmax. Multivariate analysis showed that WHO tumor grade ( $p = 0.001$ ) and SUVmax  $\geq 2.6$  ( $p < 0.001$ ) were independent predictors for tumor-related mortality, but not tumor volume or TBRmax or TBRmean. SUVmax  $\geq 2.6$  ( $p = 0.007$ ) and being treated for a recurrence rather than for a primary tumor manifestation ( $p =$

0.014) were predictors for progression-free survival, but not TBRmax or TBRmean.  
CONCLUSION: In this heterogeneous patient population, higher tracer uptake in FET-PET appears to be associated with a worse tumor-related mortality and a shorter duration of the disease-free interval.

[707]

**TÍTULO / TITLE:** - Circulating tumor cells as prognostic biomarkers in cutaneous melanoma patients.

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

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1102:513-22. doi: 10.1007/978-1-62703-727-3\_27.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-727-3\\_27](#)

**AUTORES / AUTHORS:** - Kiyohara E; Hata K; Lam S; Hoon DS

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Oncology, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA, USA.

**RESUMEN / SUMMARY:** - Detection of circulating tumor cells (CTC) in peripheral blood has been investigated for its prognostic ability, and its potential to measure the effectiveness of treatment(s) in patients with melanoma. However, a highly sensitive and specific assay is required to detect CTC in patients' blood. We have developed a multimarker quantitative real-time reverse transcriptase polymerase chain reaction (RT-qPCR) assay for detecting CTC directly from peripheral blood specimens without the need of separating CTC from leukocytes (PBL). We selected and optimized four mRNA biomarkers (MART-1/Melan-A, MAGE-A3, PAX3, and GalNAc-T) for detection and prediction of clinical outcome in melanoma patients. Our protocol has both high sensitivity and specificity for CTC in blood specimens-detecting approximately one to five melanoma cells in 10(7) PBL. We have demonstrated the significance of this assay for serial bleed assessment of CTC in clinical trials and for daily clinical usage.

[708]

**TÍTULO / TITLE:** - Association of Positive EBAG9 Immunoreactivity With Unfavorable Prognosis in Breast Cancer Patients Treated With Tamoxifen.

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

**REVISTA / JOURNAL:** - Clin Breast Cancer. 2013 Dec;13(6):465-70. doi: 10.1016/j.clbc.2013.08.015. Epub 2013 Oct 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.clbc.2013.08.015](#)

**AUTORES / AUTHORS:** - Ijichi N; Shigekawa T; Ikeda K; Miyazaki T; Horie-Inoue K; Shimizu C; Saji S; Aogi K; Tsuda H; Osaki A; Saeki T; Inoue S

**INSTITUCIÓN / INSTITUTION:** - Division of Gene Regulation and Signal Transduction, Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan.

**RESUMEN / SUMMARY:** - INTRODUCTION: Breast cancer is primarily a hormone-dependent tumor that is regulated by the status of the estrogen and progesterone receptors. We previously identified EBAG9 as an estrogen-responsive gene in MCF-7 human breast carcinoma cells. Upregulation of EBAG9 expression has been observed in several malignant tumors such as advanced breast cancers, indicating that EBAG9 might contribute to tumor progression. PATIENTS AND METHODS: In the present study, we generated a monoclonal antibody against EBAG9, and then performed

immunohistochemical analysis of EBAG9 expression in specimens obtained from breast cancer patients treated with tamoxifen as an adjuvant therapy. RESULTS: EBAG9 immunoreactivity was detected in the cytoplasm of breast cancer cells and was significantly elevated in breast cancer samples from patients who relapsed during or after adjuvant tamoxifen treatment. Positive EBAG9 immunoreactivity was significantly correlated with poor patient prognosis. CONCLUSION: These results suggest that EBAG9 expression in tumor regions is associated with an unfavorable prognosis in breast cancer patients treated with tamoxifen.

[709]

**TÍTULO / TITLE:** - Caveolin-1 in renal cell carcinoma promotes tumour cell invasion, and in co-operation with pERK predicts metastases in patients with clinically confined disease.

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

**REVISTA / JOURNAL:** - J Transl Med. 2013 Oct 11;11(1):255. doi: 10.1186/1479-5876-11-255.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1479-5876-11-255](#)

**AUTORES / AUTHORS:** - Campbell L; Al-Jayoussi G; Gutteridge R; Gumbleton N; Griffiths R; Gumbleton S; Smith MW; Griffiths DF; Gumbleton M

**INSTITUCIÓN / INSTITUTION:** - Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff CF10 3XF, UK. [gumbleton@cf.ac.uk](mailto:gumbleton@cf.ac.uk).

**RESUMEN / SUMMARY:** - BACKGROUND: Up to 40% of patients initially diagnosed with clinically-confined renal cell carcinoma (RCC) and who undergo curative surgery will nevertheless relapse with metastatic disease (mRCC) associated with poor long term survival. The discovery of novel prognostic/predictive biomarkers and drug targets is needed and in this context the aim of the current study was to investigate a putative caveolin-1/ERK signalling axis in clinically confined RCC, and to examine in a panel of RCC cell lines the effects of caveolin-1 (Cav-1) on pathological processes (invasion and growth) and select signalling pathways. METHODS: Using immunohistochemistry we assessed the expression of both Cav-1 and phosphorylated-ERK (pERK) in 176 patients with clinically confined RCC, their correlation with histological parameters and their impact upon disease-free survival. Using a panel of RCC cell lines we explored the functional effects of Cav-1 knockdown upon cell growth, cell invasion and VEGF-A secretion, as well Cav-1 regulation by cognate cell signalling pathways. RESULTS: We found a significant correlation ( $P = 0.03$ ) between Cav-1 and pERK in a cohort of patients with clinically confined disease which represented a prognostic biomarker combination ( $HR = 4.2$ ) that effectively stratified patients into low, intermediate and high risk groups with respect to relapse, even if the patients' tumours displayed low grade and/or low stage disease. In RCC cell lines Cav-1 knockdown unequivocally reduced cell invasive capacity while also displaying both pro-and anti-proliferative effects; targeted knockdown of Cav-1 also partially suppressed VEGF-A secretion in VHL-negative RCC cells. The actions of Cav-1 in the RCC cell lines appeared independent of both ERK and AKT/mTOR signalling pathways. CONCLUSION: The combined expression of Cav-1 and pERK serves as an independent biomarker signature with potential merit in RCC surveillance strategies able to predict those patients with clinically confined disease who will eventually relapse. In a panel of in-vitro RCC cells Cav-1 promotes cell invasion with variable effects on cell growth and

VEGF-A secretion. Cav-1 has potential as a therapeutic target for the prevention and treatment of mRCC.

[710]

**TÍTULO / TITLE:** - EGFR and KRAS mutations, and ALK fusions: current developments and personalized therapies for patients with advanced non-small-cell lung cancer.

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

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Nov;14(14):1765-77. doi: 10.2217/pgs.13.177.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.177](#)

**AUTORES / AUTHORS:** - de Mello RA; Madureira P; Carvalho LS; Araujo A; O'Brien M; Popat S

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Portuguese Oncology Institute, Rua Dr Antonio Bernardino de Almeida, 4200-072, Porto, Portugal.

**RESUMEN / SUMMARY:** - Personalized therapy has significantly developed in lung cancer treatment over recent years. VEGF and EGF play a major role in non-small-cell lung cancer (NSCLC) tumor angiogenesis and aggressiveness. EGFR mutation as well as KRAS and ALK rearrangements are important biomarkers in the field owing to potential targeted therapies involved in clinical practice: erlotinib, gefitinib, cetuximab and crizotinib. More recently, regulation of tumor immunity through CTLA4 and PD1/L1 has emerged as a promising field in NSCLC management. This review will focus on the current and future biomarkers in the advanced NSCLC field and also address potential related targeted therapies for these patients.

[711]

**TÍTULO / TITLE:** - The relationship between serum tumor-associated trypsin inhibitor levels and clinicopathological parameters in patients with gastric cancer.

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

**REVISTA / JOURNAL:** - Eur Rev Med Pharmacol Sci. 2013 Nov;17(21):2923-8.

**AUTORES / AUTHORS:** - Kemik O; Kemik A; Sumer A; Almali N; Gurluler E; Gures N; Purisa S; Adas G; Dogan Y; Tuzun S

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, School of Medicine, University of Yuzuncu Yil, Van, Turkey. [ozgurkemik@hotmail.com](mailto:ozgurkemik@hotmail.com)

**RESUMEN / SUMMARY:** - BACKGROUND: Tumor-associated trypsin inhibitor (TATI) is expressed with trypsinogen in tumors. We studied the clinical-pathologic association and significance of preoperative serum levels of TATI in gastric cancer patients. PATIENTS AND METHODS: Pre-treatment serum levels of TATI in patients with gastric cancer and healthy controls were analyzed by a specific enzyme-linked immunosorbent assay (ELISA). RESULTS: Statistically significant differences were found in serum TATI levels between patients with gastric cancer and healthy controls ( $p < 0.0001$ ). There was a significant relationship between the serum levels of TATI and clinicopathological parameters. However, serum levels of TATI were significantly higher in patients with an advanced T stage (T3) ( $p < 0.001$ ), lymph node metastasis ( $p < 0.001$ ) and an advanced TNM stage (stage III or IV;  $p < 0.001$ ). CONCLUSIONS: Our study suggests that TATI may be used to identify potentially high-risk groups of

upper gastric carcinoma. Elevated level of TATI was associated with progressive disease or advanced stage.

[712]

**TÍTULO / TITLE:** - Human equilibrative nucleoside transporter 1 (hENT1): Do we really have a new predictive biomarker of chemotherapy outcome in pancreatic cancer patients?

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

**REVISTA / JOURNAL:** - Pancreatology. 2013 Nov-Dec;13(6):558-63. doi: 10.1016/j.pan.2013.09.005. Epub 2013 Oct 10.

●● Enlace al texto completo (gratis o de pago) [1016/j.pan.2013.09.005](#)

**AUTORES / AUTHORS:** - Mohelnikova-Duchonova B; Melichar B

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic; Biomedical Centre, Faculty of Medicine in Plzen, Charles University in Prague, Plzen, Czech Republic. Electronic address: [beatrice.mohelnikova@gmail.com](mailto:beatrice.mohelnikova@gmail.com).

**RESUMEN / SUMMARY:** - Although systemic chemotherapy significantly improves the overall survival of pancreatic cancer patients, the prognosis remains extremely poor. The development of a drug resistance, either de novo or induced resistance, significantly limits the effectiveness of chemotherapy. SLC29A1 gene encodes human equilibrative nucleoside transporter 1 (hENT1) protein that is mediating the transport of nucleotides, both purines and pyrimidines, into the tumor cells. The aim of this mini-review is to summarize the current information concerning the prognostic and predictive role of SLC29A1 transporter (hENT1) expression in pancreatic cancer. Increased expression of SLC29A1 in vitro has been described as a potential critical factor determining the sensitivity of pancreatic cancer cells to gemcitabine and 5-fluorouracil, the principal cytotoxic agents used in the treatment of pancreatic cancer. The reports on the relationship between SLC29A1 expression and prognosis of patients with pancreatic cancer are currently rather conflicting. However, majority of studies on patients with resected pancreatic cancer have suggested that high SLC29A1 expression may be predictive of improved survival in patients treated with gemcitabine. SLC29A1 has not been shown to represent a predictive biomarker for patients treated by 5-fluorouracil. In conclusion, potential prognostic and predictive role of SLC29A1 has been demonstrated for selected subset of patients.

[713]

**TÍTULO / TITLE:** - Diagnostic and prognostic value of circulating tumor-related DNA in cancer patients.

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

**REVISTA / JOURNAL:** - Expert Rev Mol Diagn. 2013 Nov;13(8):827-44. doi: 10.1586/14737159.2013.845088. Epub 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1586/14737159.2013.845088](#)

**AUTORES / AUTHORS:** - Marzese DM; Hirose H; Hoon DS

**INSTITUCIÓN / INSTITUTION:** - Department of Molecular Oncology, John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA, 90404, USA.

**RESUMEN / SUMMARY:** - Qualitative and quantitative analysis of circulating cell-free DNA (cfDNA) is an emerging non-invasive blood biomarker utilized to assess tumor progression and to evaluate prognosis, diagnosis and response to treatment. There is a need to develop cfDNA biomarkers to avoid complex risk-prone biopsy procedures for primary or metastatic tumors. Given the challenges associated with inter- and intra-tumor heterogeneity, the implementation of genome-wide cfDNA analysis will become an important avenue to understand tumor progression and therapeutic settings, not only for predominant, but also for under-represented tumor subclones with specific genomic aberrations. We summarize the latest publications in cfDNA analysis, including a metric analysis of clinical trials and new high-throughput technology applied to cfDNA analysis in clinical oncology.

[714]

**TÍTULO / TITLE:** - Safety and Efficacy of Everolimus With Exemestane vs. Exemestane Alone in Elderly Patients With HER2-Negative, Hormone Receptor-Positive Breast Cancer in BOLERO-2.

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

**REVISTA / JOURNAL:** - Clin Breast Cancer. 2013 Dec;13(6):421-432.e8. doi: 10.1016/j.clbc.2013.08.011.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.clbc.2013.08.011](#)

**AUTORES / AUTHORS:** - Pritchard KI; Burris HA 3rd; Ito Y; Rugo HS; Dakhil S; Hortobagyi GN; Campone M; Csomos T; Baselga J; Puttawibul P; Piccart M; Heng D; Noguchi S; Srimuninnimit V; Bourgeois H; Gonzalez Martin A; Osborne K; Panneerselvam A; Taran T; Sasmoud T; Gnant M

**INSTITUCIÓN / INSTITUTION:** - Sunnybrook Odette Cancer Centre and the University of Toronto, Toronto, Ontario, Canada. Electronic address:

[Kathy.pritchard@sunnybrook.ca](mailto:Kathy.pritchard@sunnybrook.ca).

**RESUMEN / SUMMARY:** - BACKGROUND: Postmenopausal women with hormone receptor-positive (HR(+)) breast cancer in whom disease progresses or there is recurrence while taking a nonsteroidal aromatase inhibitor (NSAI) are usually treated with exemestane (EXE), but no single standard of care exists in this setting. The BOLERO-2 trial demonstrated that adding everolimus (EVE) to EXE improved progression-free survival (PFS) while maintaining quality of life when compared with EXE alone. Because many women with HR(+) advanced breast cancer are elderly, the tolerability profile of EVE plus EXE in this population is of interest. PATIENTS AND METHODS: BOLERO-2, a phase III randomized trial, compared EVE (10 mg/d) and placebo (PBO), both plus EXE (25 mg/d), in 724 postmenopausal women with HR(+) advanced breast cancer recurring/progressing after treatment with NSAIs. Safety and efficacy data in elderly patients are reported at 18-month median follow-up. RESULTS: Baseline disease characteristics and treatment histories among the elderly subsets ( $\geq 65$  years,  $n = 275$ ;  $\geq 70$  years,  $n = 164$ ) were generally comparable with younger patients. The addition of EVE to EXE improved PFS regardless of age (hazard ratio, 0.59 [ $\geq 65$  years] and 0.45 [ $\geq 70$  years]). Adverse events (AEs) of special interest (all grades) that occurred more frequently with EVE than with PBO included stomatitis, infections, rash, pneumonitis, and hyperglycemia. Elderly EVE-treated patients had similar incidences of these AEs as did younger patients but had more on-treatment deaths. CONCLUSION: Adding EVE to EXE offers substantially improved PFS over

EXE and was generally well tolerated in elderly patients with HR(+) advanced breast cancer. Careful monitoring and appropriate dose reductions or interruptions for AE management are recommended during treatment with EVE in this patient population.

[715]

**TÍTULO / TITLE:** - Weight gain and tumour necrosis factor-alpha inhibitors in patients with psoriasis.

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

**REVISTA / JOURNAL:** - Australas J Dermatol. 2013 Nov;54(4):259-63. doi: 10.1111/ajd.12044.

●● Enlace al texto completo (gratis o de pago) [1111/ajd.12044](#)

**AUTORES / AUTHORS:** - Tan E; Baker C; Foley P

**INSTITUCIÓN / INSTITUTION:** - Skin and Cancer Foundation Victoria, Carlton, Victoria, Australia.

**RESUMEN / SUMMARY:** - OBJECTIVES: To compare the effect of anti-tumour necrosis factor (TNF)-alpha therapies with agents that do not target TNF-alpha on bodyweight and body mass index (BMI) in patients with psoriasis. METHODS: A retrospective analysis of patients from the Skin and Cancer Foundation and St Vincent's Hospital Melbourne. Bodyweight and BMI were compared at baseline and weeks 12, 24 and 48. RESULTS: A total of 143 patients were studied, equating 286 treatment courses in all. Of these, 178 courses were with an anti-TNFalpha agent (54 on adalimumab, 61 on etanercept and 63 on infliximab) and 108 courses were on non-anti-TNFalpha agents (73 on efalizumab and 35 on ustekinumab). Anti-TNFalpha therapy with adalimumab and infliximab resulted in weight gain from week 12 until week 48. At week 12 the infliximab group gained 1.7 +/- 4.7 kg and adalimumab group gained 1.5k +/- 4.5 kg. This effect persisted at week 24 (infliximab: 3.4 +/- 5.7 kg; adalimumab: 2.2 +/- 4.4 kg) until the end of the study (infliximab: 1.3 +/- 2.9 kg; adalimumab: 2.4 +/- 6.4 kg). There was a trend for weight gain in the etanercept group that did not reach statistical significance. Therapy with ustekinumab and efalizumab did not result in weight gain. CONCLUSION: Therapy with adalimumab and infliximab is associated with a significant increase in bodyweight and BMI.

[716]

**TÍTULO / TITLE:** - Resistance to tyrosine kinase inhibitors in clear cell renal cell carcinoma: From the patient's bed to molecular mechanisms.

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

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 Oct 14. pii: S0304-419X(13)00043-7. doi: 10.1016/j.bbcan.2013.10.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbcan.2013.10.001](#)

**AUTORES / AUTHORS:** - Buczek M; Escudier B; Bartnik E; Szczylik C; Czarnecka A

**INSTITUCIÓN / INSTITUTION:** - Military Institute of Medicine, Warsaw, Poland.

Electronic address: [mbuczek86@gmail.com](mailto:mbuczek86@gmail.com).

**RESUMEN / SUMMARY:** - The introduction of anti-angiogenic drugs especially tyrosine kinase inhibitors (TKIs) was a breakthrough in the treatment of renal cell carcinoma (RCC). Although TKIs have significantly improved outcome in patients with metastatic disease, the majority still develop resistance over time. Because different combinations

and sequences of TKIs are tested in clinical trials, resistance patterns and mechanisms underlying this phenomenon should be thoroughly investigated. From a clinical point of view, resistance occurs either as a primary phenomenon (intrinsic) or as a secondary phenomenon related to various escape/evasive mechanisms that the tumor develops in response to vascular endothelial growth factor (VEGF) inhibition. Intrinsic resistance is less common, and related to the primary redundancy of available angiogenic signals from the tumor, causing unresponsiveness to VEGF-targeted therapies. Acquired resistance in tumors is associated with activation of an angiogenic switch which leads to either upregulation of the existing VEGF pathway or recruitment of alternative factors responsible for tumor revascularization. Multiple mechanisms can be involved in different tumor settings that contribute both to evasive and intrinsic resistance, and current endeavor aims to identify these processes and assess their importance in clinical settings and design of pharmacological strategies that lead to enduring anti-angiogenic therapies.

[717]

**TÍTULO / TITLE:** - mRNA expression profile of multidrug resistant genes in acute lymphoblastic leukemia of children, a prognostic value for ABCA3 and ABCA2.

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

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Oct 21;15(1).

**AUTORES / AUTHORS:** - Rahgozar S; Moafi A; Abedi M; Entezar-E-Ghaem M; Moshtaghian J; Ghaedi K; Esmailie A; Montazeri M

**INSTITUCIÓN / INSTITUTION:** - Division of Cell and Molecular Biology; Department of Biology; Faculty of Science; University of Isfahan; Isfahan, Iran.

**RESUMEN / SUMMARY:** - Multidrug resistance (MDR) is an important cause of treatment failure in acute lymphoblastic leukemia (ALL). The ABC family of membrane transporters is proposed, albeit with controversy, to be involved in this process. The present study aims to investigate the mRNA expression profile of several genes of this family, including ABCA2, ABCA3, ABCB1/MDR1, MRP1/ABCC1, MRP3/ABCC3, ABCG2/BCRP, and the intracellular transporter MVP/LRP, in childhood ALL, and to evaluate their association with response to therapy. Some genes in the present research are being studied for the first time in Iran. Using quantitative real time PCR, we evaluated 27 children with ALL at diagnosis and 15 children with normal bone marrow. The status of response to therapy was assessed one year after the onset of therapy through investigating the IgH/TCRgamma gene rearrangements. Our findings indicate a considerable and direct relationship between mRNA expression levels of ABCA2, ABCA3, MDR1, and MRP1 genes and positive minimal residual disease (MRD) measured after one-year treatment. Statistical analysis revealed that expression of these genes higher than the cutoff point will raise the risk of MRD by 15-, 6.25-, 12-, and 9-fold, respectively. No relationship was found between of MVP/LRP, MRP3 and ABCG2 genes expression and ALL prognoses. Considering the direct and significant relationship between the increased expression of ABCA2, ABCA3, MDR1, and MRP1 genes and positive risk of MRD in children with ALL, evaluating the expression profile of these genes on diagnosis may identify high risk individuals and help plan a more efficient treatment strategy.

[718]

**TÍTULO / TITLE:** - Prognostic value of serum Tie-2 and vascular endothelial growth factor levels in cancer patients.

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

**REVISTA / JOURNAL:** - Eur Rev Med Pharmacol Sci. 2013 Nov;17(21):2929-32.

**AUTORES / AUTHORS:** - Seker MM; Sancaktar E; Acibucu DO; Filiz AK; Deveci K; Bahceci A; Kacan T; Babacan N; Yuce S

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Department of Biochemistry, Department of Physiology, Department of Ear & Nose & Throat, Cumhuriyet University Faculty of Medicine, Sivas, Turkey. [mmetinseker@yahoo.com.tr](mailto:mmetinseker@yahoo.com.tr)

**RESUMEN / SUMMARY:** - BACKGROUND: Angiogenesis is a very essential process in tumor biology. Vascular endothelial growth factor (VEGF), angiopoietin and its receptor (TIE-2) are very important mediators for angiogenesis. In this trial, we aimed to analyze the role of these mediators on chemotherapy response and survival. PATIENTS AND METHODS: Forty four cancer patients and 22 healthy controls were included in the study. Baseline serum samples were obtained from all participants and post-chemotherapy serum samples were obtained from the cancer patients. Serum vascular endothelial growth factor and TIE-2 levels were measured with quantitative enzyme-linked immunosorbent assay techniques. RESULTS: The baseline serum vascular endothelial growth factor level was 187.5 and 120.2 pg/ml in cancer patients and the control group ( $p = 0.006$ ). The baseline serum TIE-2 level was 615.9 and 242.5 pg/ml in the patients and control group ( $p < 0.001$ ). There was a significant difference between patients' baseline and post-chemotherapy VEGF levels (111.9 pg/ml;  $p < 0.001$ ) and patients' baseline and post-chemotherapy TIE-2 levels (344.5 pg/ml;  $p < 0.001$ ). The overall survival rate was better in patients who had lower baseline VEGF and TIE-2 levels and whose TIE-2 level had decreased with chemotherapy. CONCLUSIONS: Higher baseline TIE-2 and VEGF levels are related and worsen survival. Decreasing levels of TIE-2, but not VEGF, which, with chemotherapy, may be predictive for survival.

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[719]

**TÍTULO / TITLE:** - Tumor angiogenesis genotyping and efficacy of first-line chemotherapy in metastatic gastric cancer patients.

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

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Dec;14(16):1991-8. doi: 10.2217/pgs.13.185. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.185](#)

**AUTORES / AUTHORS:** - Scartozzi M; Giampieri R; Loretelli C; Bittoni A; Mandolesi A; Faloppi L; Bianconi M; Del Prete M; Andrikou K; Bearzi I; Cascinu S

**INSTITUCIÓN / INSTITUTION:** - Department of Clinica di Oncologia Medica, AO Ospedali Riuniti-Universita Politecnica delle Marche, Ancona, Italy.

**RESUMEN / SUMMARY:** - Aim: Besides correlating with prognosis, tumor-driven angiogenesis also seemed able to influence response/resistance to chemotherapy in preclinical models. We examined the role of tumor angiogenesis genotyping in determining clinical outcome in metastatic gastric cancer patients receiving first-line chemotherapy. Patients & methods: VEGF-A, VEGF-C, FLT1, KDR and FLT4 genotyping was analyzed in gastric tumors from patients receiving platinum-based

first-line chemotherapy. Results: VEGF-A rs25648 correlated with response rate (partial response: 18% among patients showing the VEGF-A rs25648 CT or TT genotype vs 44% among patients showing the VEGF-A rs25648 C genotype;  $p = 0.04$ ). At multivariate analysis only VEGF-A rs25648 maintained an independent role in determining median progression-free survival (hazard ratio: 1.65 95% CI: 1.12-2.78) and overall survival (hazard ratio: 1.58, 95% CI: 1.17-2.65). Conclusion: VEGF-A rs25648 genotyping may help identify a patient subgroup unlikely to benefit from a first-line, platinum-based combination and potential candidates for alternative therapy choices. Original submitted 26 July 2013; Revision submitted 16 September 2013; Published online 3 October 2013.

[720]

**TÍTULO / TITLE:** - FHIT, EGFR, and MSH2: Possible Etiopathologic, Prognostic, and Predictive Role in Non-Small Cell Lung Carcinoma in Egyptian Patients.

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

**REVISTA / JOURNAL:** - Appl Immunohistochem Mol Morphol. 2013 Oct 31.

●● Enlace al texto completo (gratis o de pago) [1097/PAI.0b013e3182988fa5](#)

**AUTORES / AUTHORS:** - Younes SF; Aiad HA; Asaad NY; Natkunam Y; Mokhtar NM

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**RESUMEN / SUMMARY:** - The high incidence and mortality of lung carcinoma in Egypt necessitates studying the factors that may be implicated in non-small cell lung carcinoma (NSCLC) pathogenesis and could affect patient management. The aim was to study FHIT, epidermal growth factor receptor (EGFR), and MSH2 protein expression in Egyptian patients with NSCLC. Immunohistochemical staining for FHIT, EGFR, and MSH2 was performed on 64 specimens from NSCLC patients and correlated with prognostic parameters, response to therapy, and overall survival. FHIT loss was observed in 64% of NSCLC patients and was significantly associated with SCC ( $P=0.003$ ) and poor tumor grade ( $P=0.043$ ). EGFR overexpression was observed in 47% of NSCLC patients and was significantly associated with SCC ( $P=0.002$ ). MSH2 was reduced in 23.4% of NSCLC patients and was significantly associated with adenocarcinoma ( $P=0.024$ ). In a univariate analysis, a significant relationship was seen between the poor overall survival in NSCLC patients and high T-stage ( $P=0.029$ ), presence of metastasis ( $P=0.014$ ), advanced-stage grouping ( $P=0.004$ ), and FHIT loss ( $P=0.033$ ). Further, FHIT loss was significantly related to disease progression in patients treated with chemotherapy ( $P=0.038$ ). We conclude that all 3 markers play a role in the development of NSCLC in Egyptian patients. We suggest that FHIT loss be used as a predictor for progression in chemotherapy-treated NSCLC patients.

[721]

**TÍTULO / TITLE:** - Amurensin G enhances the susceptibility to tumor necrosis factor-related apoptosis-inducing ligand-mediated cytotoxicity of cancer stem-like cells of HCT-15 cells.

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

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Oct 5. doi: 10.1111/cas.12299.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12299](https://doi.org/10.1111/cas.12299)

**AUTORES / AUTHORS:** - Lee SH; Kim MJ; Kim DW; Kang CD; Kim SH

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Medical Research Institute, Pusan National University School of Medicine, Yangsan, Korea.

**RESUMEN / SUMMARY:** - Cancer stem cells (CSCs) are resistant to radiotherapy and chemotherapy and play a significant role in cancer recurrence. Design of better treatment strategies that can eliminate or otherwise control CSC populations in tumors is necessary. In this study, the sensitivity to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced cytotoxicity and the effect of amurensin G, a novel sirtuin 1 (SIRT1) inhibitor, were examined using the CSC-enriched fraction of HCT-15 human colon cancer cells. Cancer stem cell-enriched HCT-15 colony cells were paradoxically less sensitive to doxorubicin, and more sensitive to TRAIL-induced cytotoxicity, than their parental cells. Also, CD44+ HCT-15 cells were more susceptible to TRAIL-mediated cytotoxicity than CD44- HCT-15 cells, possibly due to increased levels of death receptors DR4 and DR5 as well as c-Myc, and decreased levels of c-FLIPL /S in CD44+ cells compared with CD44- HCT-15 cells. The combination effect of amurensin G on TRAIL-mediated cytotoxicity was much more apparent in CD44+ cells than in CD44- HCT-15 cells, and this was associated with more prominent downregulation of c-FLIPL /S in CD44+ cells than in CD44- HCT-15 cells. These results indicate that HCT-15 colony or CD44+ cells, which may have CSC properties, are more sensitive to TRAIL than parental or CD44- HCT-15 cells. Amurensin G may be effective in eliminating colon CSCs and be applicable to potentiate the sensitivity of colon CSCs to TRAIL.

[722]

**TÍTULO / TITLE:** - Efficacy of the dual PI3K and mTOR inhibitor NVP-BEZ235 in combination with nilotinib against BCR-ABL-positive leukemia cells involves the ABL kinase domain mutation.

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

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Oct 7;15(2).

**AUTORES / AUTHORS:** - Okabe S; Tauchi T; Tanaka Y; Kitahara T; Kimura S; Maekawa T; Ohyashiki K

**INSTITUCIÓN / INSTITUTION:** - First Department of Internal Medicine; Tokyo Medical University; Tokyo, Japan.

**RESUMEN / SUMMARY:** - Imatinib, an ABL tyrosine kinase inhibitor (TKI), has shown clinical efficacy against chronic myeloid leukemia (CML). However, a substantial number of patients develop resistance to imatinib treatment due to the emergence of clones carrying mutations in the protein BCR-ABL. The phosphoinositide 3 kinase (PI3K)/Akt /mammalian target of rapamycin (mTOR) pathway regulates various processes, including cell proliferation, cell survival and antiapoptosis activity. In this study, we investigated the efficacy of NVP-BEZ235, a dual PI3K and mTOR inhibitor, using BCR-ABL-positive cell lines. Treatment with NVP-BEZ235 for 48 h inhibited cell growth and induced apoptosis. The phosphorylation of the AKT kinase, eukaryotic initiation factor 4-binding protein 1 (4E-BP1), and p70 S6 kinase were decreased after NVP-BEZ235 treatment. The combination of NVP-BEZ235 with a BCR-ABL kinase inhibitor, imatinib or nilotinib, induced a more pronounced colony growth inhibition,

whereas the combination of NVP-BEZ235 and nilotinib was more effective in inducing apoptosis and reducing the phosphorylation of AKT, 4E-BP1, and S6 kinase. NVP-BEZ235 in combination with nilotinib also inhibited tumor growth in a xenograft model and inhibited the growth of primary T315I mutant cells and ponatinib-resistant cells. Taken together, these results suggest that administration of the dual PI3K and mTOR inhibitor NVP-BEZ235 may be an effective strategy against BCR-ABL mutant cells and may enhance the cytotoxic effects of nilotinib in ABL TKI-resistant BCR-ABL mutant cells.

[723]

**TÍTULO / TITLE:** - Nonsteroidal anti-inflammatory drug sulindac sulfide suppresses structural protein Nesprin-2 expression in colorectal cancer cells.

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

**REVISTA / JOURNAL:** - Biochim Biophys Acta. 2013 Sep 27;1840(1):322-331. doi: 10.1016/j.bbagen.2013.09.032.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbagen.2013.09.032](#)

**AUTORES / AUTHORS:** - Liggett JL; Choi CK; Donnell RL; Kihm KD; Kim JS; Min KW; Noegel AA; Baek SJ

**INSTITUCIÓN / INSTITUTION:** - Department of Biomedical and Diagnostic Sciences, University of Tennessee, Knoxville, TN 37996, USA.

**RESUMEN / SUMMARY:** - BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known for treating inflammatory disease and have been reported to have anti-tumorigenic effects. Their mechanisms are not fully understood, but both cyclooxygenase (COX) dependent and independent pathways are involved. Our goal was to shed further light on COX-independent activity. METHODS: Human colorectal cancer cells were observed under differential interference contrast microscopy (DICM), fluorescent microscopy, and micro-impedance measurement. Microarray analysis was performed using HCT-116 cells treated with sulindac sulfide (SS). PCR and Western blots were performed to confirm the microarray data and immunohistochemistry was performed to screen for Nesprin-2 expression. Micro-impedance was repeating including Nesprin-2 knock-down by siRNA. RESULTS: HCT-116 cells treated with SS showed dramatic morphological changes under DICM and fluorescent microscopy, as well as weakened cellular adhesion as measured by micro-impedance. Nesprin-2 was selected from two independent microarrays, based on its novelty in relation to cancer and its role in cell organization. SS diminished Nesprin-2 mRNA expression as assessed by reverse transcriptase and real time PCR. Various other NSAIDs were also tested and demonstrated that inhibition of Nesprin-2 mRNA was not unique to SS. Additionally, immunohistochemistry showed higher levels of Nesprin-2 in many tumors in comparison with normal tissues. Further micro-impedance experiments on cells with reduced Nesprin-2 expression showed a proportional loss of cellular adhesion. CONCLUSIONS: Nesprin-2 is down-regulated by NSAIDs and highly expressed in many cancers. GENERAL SIGNIFICANCE: Our data suggest that Nesprin-2 may be a potential novel oncogene in human cancer cells and NSAIDs could decrease its expression.

[724]

**TÍTULO / TITLE:** - Fas Gene Variants in Childhood Acute Lymphoblastic Leukemia and Association with Prognosis.

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

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [1007/s12253-013-9705-2](#)

**AUTORES / AUTHORS:** - Valibeigi B; Amirghofran Z; Golmoghaddam H; Hajhosseini R; Kamazani FM

**INSTITUCIÓN / INSTITUTION:** - Payame Noor University, Tehran Center, Tehran, Iran.

**RESUMEN / SUMMARY:** - Fas molecule is one of the main important molecules involved in apoptotic cell death. Single nucleotide polymorphisms in the promoter of Fas gene at positions -1377G/A and -670 A/G may affect its expression and play an important role in the pathology of leukemia. In the present study the association between these polymorphisms and risk of the development of acute lymphoblastic leukemia (ALL) in children with ALL compared to cancer-free control subjects was examined by polymerase chain reaction- based restriction fragment length polymorphism. The relationship between the polymorphisms and clinical and laboratory features of the patients and response to therapy were determined. No significant differences in genotype and allele frequencies between the patients and the control subjects at positions -670 and -1377 were detected. Evaluation of the prognostic factors revealed an association between the GG genotype at position -670 and liver involvement in ALL patients ( $p < 0.04$ ). Although patients with -1377 AA genotype showed shorter mean complete remission duration, the result of survival analysis did not reach to be significant. In conclusion, results of this study showed no contribution of Fas genotypes at positions -670 and -1377 to risk of ALL in children. The association of Fas GG genotype at position -670 with liver involvement in the patients may show its important role in prognosis of ALL.

[725]

**TÍTULO / TITLE:** - Comprehensive analysis of the percentage of surface receptors and cytotoxic granules positive natural killer cells in patients with pancreatic cancer, gastric cancer, and colorectal cancer.

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

**REVISTA / JOURNAL:** - J Transl Med. 2013 Oct 20;11(1):262.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-262](#)

**AUTORES / AUTHORS:** - Peng YP; Zhu Y; Zhang JJ; Xu ZK; Qian ZY; Dai CC; Jiang KR; Wu JL; Gao WT; Li Q; Du Q; Miao Y

**RESUMEN / SUMMARY:** - BACKGROUND: Digestive malignancies, especially pancreatic cancer (PC), gastric cancer (GC), and colorectal cancer (CRC), still occur at persistently high rates, and disease progression in these cancers has been associated with tumor immunosurveillance escape. Natural killer (NK) cell dysfunction may be responsible for this phenomenon, however, the exact relationship between tumor immunosurveillance escape in digestive malignancies and NK cell dysfunction remains unclear. METHODS: Percentage of the surface receptors NKG2A, KIR3DL1, NKG2D, NKp30, NKp44, NKp46, and DNAM-1, as well as the cytotoxic granules perforin and granzyme B positive NK cells were determined in patients with pancreatic cancer ( $n = 31$ ), gastric cancer ( $n = 31$ ), and CRC ( $n = 32$ ) prior to surgery and healthy controls ( $n = 31$ ) by multicolor flow cytometry. Independent t-tests or Mann-Whitney U-tests were

used to compare the differences between the patient and healthy control groups, as well as the differences between patients with different pathologic features of cancer. RESULTS: Percentage of NKG2D, NKp30, NKp46, and perforin positive NK cells was significantly down-regulated in patients with PC compared to healthy controls, as well as GC and CRC; reduced levels of these molecules was associated with indicators of disease progression in each malignancy (such as histological grade, depth of invasion, lymph node metastasis). On the contrary, percentage of KIR3DL1 positive NK cells was significantly increased in patients with PC, as well as GC and CRC, but was not associated with any indicators of disease progression. CONCLUSIONS: Altered percentage of surface receptors and cytotoxic granules positive NK cells may play a vital role in tumor immunosurveillance escape by inducing NK cell dysfunction in patients with PC, GC, and CRC.

[726]

**TÍTULO / TITLE:** - AGR2 Predicts Tamoxifen Resistance in Postmenopausal Breast Cancer Patients.

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

**REVISTA / JOURNAL:** - Dis Markers. 2013;35(4):207-12. doi: 10.1155/2013/761537. Epub 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1155/2013/761537](#)

**AUTORES / AUTHORS:** - Hrstka R; Brychtova V; Fabian P; Vojtesek B; Svoboda M

**INSTITUCIÓN / INSTITUTION:** - Regional Centre for Applied Molecular Oncology, Masaryk Memorial Cancer Institute, Zluty kopec 7, 656 53 Brno, Czech Republic.

**RESUMEN / SUMMARY:** - Endocrine resistance is a significant problem in breast cancer treatment. Thus identification and validation of novel resistance determinants is important to improve treatment efficacy and patient outcome. In our work, AGR2 expression was determined by qRT-PCR in Tru-Cut needle biopsies from tamoxifen-treated postmenopausal breast cancer patients. Our results showed inverted association of AGR2 mRNA levels with primary treatment response ( $P = 0.0011$ ) and progression-free survival ( $P = 0.0366$ ) in 61 ER-positive breast carcinomas. As shown by our experimental and clinical evaluations, elevated AGR2 expression predicts decreased efficacy of tamoxifen treatment. From this perspective, AGR2 is a potential predictive biomarker enabling selection of an optimal algorithm for adjuvant hormonal therapy in postmenopausal ER-positive breast cancer patients.

[727]

**TÍTULO / TITLE:** - Hsp90 inhibitor BIIB021 enhances triptolide-induced apoptosis of human T-cell acute lymphoblastic leukemia cells in vitro mainly by disrupting p53-MDM2 balance.

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

**REVISTA / JOURNAL:** - Acta Pharmacol Sin. 2013 Nov 18. doi: 10.1038/aps.2013.124.

●● Enlace al texto completo (gratis o de pago) [1038/aps.2013.124](#)

**AUTORES / AUTHORS:** - Li M; Zhang X; Zhou WJ; Chen YH; Liu H; Liu L; Yang CM; Qan WB

**INSTITUCIÓN / INSTITUTION:** - Institute of Hematology, the First Affiliated Hospital, College of Medicine, Zhejiang University, Zhejiang 310003, China.

**RESUMEN / SUMMARY:** - Aim: To investigate the effects of BIIB021, an inhibitor of heat shock protein 90 (Hsp90) alone or in combination with triptolide (TPL) on T-cell acute lymphoblastic leukemia (T-ALL) and the mechanisms of action. Methods: Human T-ALL cells line Molt-4 was examined. The cell viability was measured using MTT assay. Apoptotic cells were studied with Hoechst 33258 staining. Cell apoptosis and cell cycle were analyzed using flow cytometry with Annexin V/PI staining and PI staining, respectively. The levels of multiple proteins, including Akt, p65, CDK4/6, p18, Bcl-2 family proteins, MDM2, and p53, were examined with Western blotting. The level of MDM2 mRNA was determined using RT-PCR. Results: Treatment of Molt-4 cells with BIIB021 (50-800 nmol/L) inhibited the cell growth in a dose-dependent manner (the IC50 value was 384.6 and 301.8 nmol/L, respectively, at 48 and 72 h). BIIB021 dose-dependently induced G0/G1 phase arrest, followed by apoptosis of Molt-4 cells. Furthermore, BIIB021 increased the expression of p18, decreased the expression of CDK4/6, and activated the caspase pathway in Molt-4 cells. Moreover, BIIB021 (50-400 nmol/L) dose-dependently decreased the phospho-MDM2 and total MDM2 protein levels, but slightly increased the phospho-p53 and total p53 protein levels, whereas TPL (5-40 nmol/L) dose-dependently enhanced p53 activation without affecting MDM2 levels. Co-treatment with BIIB021 and TPL showed synergic inhibition on Molt-4 cell growth. The co-treatment disrupted p53-MDM2 balance, thus markedly enhanced p53 activation. In addition, the co-treatment increased the expression of Bak and Bim, followed by increased activation of caspase-9. Conclusion: The combination of BIIB021 and TPL may provide a novel strategy for treating T-ALL by overcoming multiple mechanisms of apoptosis resistance.

[728]

**TÍTULO / TITLE:** - PQJS380: A novel lead compound to induce apoptosis in acute lymphoblastic leukemia cells.

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

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Nov 19;15(1).

**AUTORES / AUTHORS:** - Zhu X; Chen L; Sheng J; Chen C; Yao Y; Chen D; Xue H; Pan J

**INSTITUCIÓN / INSTITUTION:** - Department of Pathophysiology; Zhongshan School of Medicine; Sun Yat-sen University; Guangzhou, PR China; Key Laboratory of Tropical Disease Control; Sun Yat-sen University; Ministry of Education; Guangzhou, PR China.

**RESUMEN / SUMMARY:** - Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid progenitor cells that are committed to the B- or the T-cell lineage. The pathogenesis of ALL is heterogeneous and may be at least in part caused by genetic alterations. Although the modern sequencing technologies make it possible to rapidly discover novel genetic and epigenetic alterations and molecular targets for therapeutic intervention for ALL, conventional chemotherapy is still the most important therapeutic approach. Relapses and high morbidity and mortality remain major challenges particularly in adult patients with ALL. Therefore, development of novel chemotherapeutic agents remains in demand for ALL patients. In the course of seeking novel agents against ALL, we screened a library of small molecules and identified that PQJS380, a S-(E)-4-([7S,10S]-4-ethyl-7-isopropyl-2,5,8,12-tetraoxo-9-oxa-3,6,13,18-tetraaza-bicyclo[13,2,1]octadec-1-en-10-yl)but-3-enyl octanethioate, showed potent

anti-leukemia activity. PQJS380 inhibited the proliferation with IC 50 values of 14.25 nM and 5 nM in REH and NALM-6 cells, respectively. PQJS380 had 10-fold higher molar potency than the front-line ALL drugs Ara-C and VP-16. The median IC 50 value for leukemia blast cells from 14 patients with ALL was 40 nM. PQJS380 induced G 1-phase arrest in REH cells, and S-phase in NALM-6 cells, respectively. Treatment of PQJS380 led to apoptosis in ALL cell lines (REH and NALM-6) cells and primary ALL cells. Our data supported that PQJS380 may be a promising lead compound for ALL treatment even though the precise targets remain to be elucidated.

[729]

**TÍTULO / TITLE:** - The value of progesterone receptor expression in predicting the Recurrence Score for hormone-receptor positive invasive breast cancer patients.

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

**REVISTA / JOURNAL:** - Breast Cancer. 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago) [1007/s12282-013-0495-x](#)

**AUTORES / AUTHORS:** - Onoda T; Yamauchi H; Yagata H; Tsugawa K; Hayashi N; Yoshida A; Suzuki K; Sakurai O; Nakamura S

**INSTITUCIÓN / INSTITUTION:** - Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan, [onodato@gmail.com](mailto:onodato@gmail.com).

**RESUMEN / SUMMARY:** - BACKGROUND: OncotypeDX® (ODX) is a well-validated assay for breast cancer treatment planning. We explored whether the conventional pathological factors could pick up high risk patients without the help of the ODX. METHODS: The ODX was performed on 139 hormone receptor-positive invasive breast cancers in a single Japanese institution. The recurrence risk was compared between the ODX and the St. Gallen Consensus. The correlations were analyzed between the Recurrence Score (RS) measured by ODX and the pathological factors. In addition, we performed a follow-up survey and examined the association of the RS with the confirmed recurrence or death. RESULTS: The ODX classified 68 (49 %) as low RS, 52 (37 %) as intermediate RS, and 19 (14 %) as high RS cases. Correlations were noted between RS and progesterone receptor (PR) ( $r = -0.53$ ), Ki-67 ( $r = 0.42$ ), and nuclear grade (NG) ( $r = 0.41$ ). None had a high RS with PR(3+) or NG1. Only one high RS patient had a Ki-67 (<20 %). The combinations of high RS with PR(0)/Ki-67 ( $\geq 20$  %) and PR(1+)/Ki-67 ( $\geq 20$  %) were 70 and 58 %, respectively. The combinations with high RS and PR(0)/NG3, PR(0)/NG2, and PR(1+)/NG3 were 83, 75, and 75 %, respectively. The median follow-up was 39.1 months (range 24.0-67.8). There were one low RS (1 %), four intermediate RS (8 %), and three high RS patients (16 %) who developed local or distant recurrence. CONCLUSION: Hormone receptor-positive invasive breast cancers are stratified with the combinations of PR/Ki-67 or PR/NG. Some of the high recurrence risk cases might be identified without the ODX.

[730]

**TÍTULO / TITLE:** - Natural killer cell therapy and aerosol interleukin-2 for the treatment of osteosarcoma lung metastasis.

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

**REVISTA / JOURNAL:** - Pediatr Blood Cancer. 2013 Oct 18. doi: 10.1002/pbc.24801.

●● Enlace al texto completo (gratis o de pago) [1002/pbc.24801](#)

**AUTORES / AUTHORS:** - Guma SR; Lee DA; Yu L; Gordon N; Hughes D; Stewart J; Wang WL; Kleinerman ES

**INSTITUCIÓN / INSTITUTION:** - Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas.

**RESUMEN / SUMMARY:** - BACKGROUND: Survival of patients with osteosarcoma lung metastases has not improved in 20 years. We evaluated the efficacy of combining natural killer (NK) cells with aerosol interleukin-2 (IL-2) to achieve organ-specific NK cell migration and expansion in the metastatic organ, and to decrease toxicity associated with systemic IL-2. PROCEDURE: Five human osteosarcoma cell lines and 103 patient samples (47 primary and 56 metastatic) were analyzed for NKG2D ligand (NKG2DL) expression. Therapeutic efficacy of aerosol IL-2 + NK cells was evaluated in vivo compared with aerosol IL-2 alone and NK cells without aerosol IL-2. RESULTS: Osteosarcoma cell lines and patient samples expressed various levels of NKG2DL. NK-mediated killing was NKG2DL-dependent and correlated with expression levels. Aerosol IL-2 increased NK cell numbers in the lung and within metastatic nodules but not in other organs. Therapeutic efficacy, as judged by tumor number, size, and quantification of apoptosis, was also increased compared with NK cells or aerosol IL-2 alone. There were no IL-2-associated systemic toxicities. CONCLUSION: Aerosol IL-2 augmented the efficacy of NK cell therapy against osteosarcoma lung metastasis, without inducing systemic toxicity. Our data suggest that lung-targeted IL-2 delivery circumvents toxicities induced by systemic administration. Combining aerosol IL-2 with NK cell infusions, may be a potential new therapeutic approach for patients with osteosarcoma lung metastasis. *Pediatr Blood Cancer* © 2013 Wiley Periodicals, Inc.

[731]

**TÍTULO / TITLE:** - 6-Shogaol induces apoptosis in human leukemia cells through a process involving caspase-mediated cleavage of eIF2alpha.

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

**REVISTA / JOURNAL:** - *Mol Cancer*. 2013 Nov 12;12(1):135.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1476-4598-12-135](#)

**AUTORES / AUTHORS:** - Liu Q; Peng YB; Zhou P; Qi LW; Zhang M; Gao N; Liu EH; Li P

**RESUMEN / SUMMARY:** - BACKGROUND: 6-Shogaol is a promising antitumor agent isolated from dietary ginger (*Zingiber officinale*). However, little is known about the efficacy of 6-shogaol on leukemia cells. Here we investigated the underlying mechanism of 6-shogaol induced apoptosis in human leukemia cells in vitro and in vivo. METHODS: Three leukemia cell lines and primary leukemia cells were used to investigate the apoptosis effect of 6-shogaol. A shotgun approach based on label-free proteome with LC-CHIP Q-TOF MS/MS was employed to identify the cellular targets of 6-shogaol and the differentially expressed proteins were analyzed by bioinformatics protocols. RESULTS: The present study indicated that 6-shogaol selectively induced apoptosis in transformed and primary leukemia cells but not in normal cells. Eukaryotic translation initiation factor 2 alpha (eIF2alpha), a key regulator in apoptosis signaling pathway, was significantly affected in both Jurkat and U937 proteome profiles. The docking results suggested that 6-shogaol might bind well to eIF2alpha at Ser51 of the N-terminal domain. Immunoblotting data indicated that 6-shogaol induced apoptosis through a process involving dephosphorylation of eIF2alpha and caspase activation—

dependent cleavage of eIF2alpha. Furthermore, 6-shogaol markedly inhibited tumor growth and induced apoptosis in U937 xenograft mouse model. CONCLUSION: The potent anti-leukemia activity of 6-shogaol found both in vitro and in vivo in our study make this compound a potential anti-tumor agent for hematologic malignancies.

[732]

**TÍTULO / TITLE:** - Synergistic Effect of 5-Azacytidine and NF-kappaB Inhibitor DHMEQ on Apoptosis Induction in Myeloid Leukemia Cells.

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

**REVISTA / JOURNAL:** - Oncol Res. 2013;20(12):571-7. doi: 10.3727/096504013X13775486749371.

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

[3727/096504013X13775486749371](#)

**AUTORES / AUTHORS:** - Togano T; Nakashima M; Watanabe M; Umezawa K; Watanabe T; Higashihara M; Horie R

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, School of Medicine, Kitasato University, Minami-ku, Sagami-hara, Kanagawa, Japan.

**RESUMEN / SUMMARY:** - Constitutive NF-kappaB activation characterizes a subset of myeloid leukemia (ML) cells. Recent reports have indicated that DNA methyltransferase (DNMT) inhibitors are alternative candidates for the treatment of ML. However, the optimal use of DNMT as a chemotherapeutic agent against ML has yet to be established. In this report, we examined the effect of the NF-kappaB inhibitor dehydroxymethylepoxyquinomicin (DHMEQ) and its combinational use with the DNMT inhibitor 5-azacytidine (AZA) in ML cell lines. DHMEQ alone induced cell death in ML cell lines with NF-kappaB activation, although the response varied among the cell lines. The addition of DHMEQ enhanced the effect of AZA on the viability and apoptosis induction of ML cell lines. The treatment of ML cell lines with AZA marginally induced NF-kappaB binding activity, although the treatment induced NF-kappaB protein. These results indicate the potential usefulness of DHMEQ and its combinational use with AZA in the treatment of ML, although the molecular effect by AZA on the NF-kappaB pathway awaits further study.

[733]

**TÍTULO / TITLE:** - Study on human promyelocytic leukemia HL-60 cells apoptosis induced by fucosterol.

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

**REVISTA / JOURNAL:** - Biomed Mater Eng. 2014;24(1):845-51. doi: 10.3233/BME-130876.

●● Enlace al texto completo (gratis o de pago) [3233/BME-130876](#)

**AUTORES / AUTHORS:** - Ji YB; Ji CF; Yue L

**INSTITUCIÓN / INSTITUTION:** - Engineering Research Center of Natural Anticancer Drugs, Ministry of Education, Harbin University of Commerce, Harbin, China.

**RESUMEN / SUMMARY:** - In this study, we investigated the effect of fucosterol on HL-60 and the molecular mechanism. HL-60 Cells were treated with fucosterol, and 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method was used to study fucosterol anti-tumor activity. Morphology of HL-60 cells was observed. Flow

cytometry (FCM) was employed to detect the cell cycle. Laser scanning confocal microscope (LSCM) was used to analyze mitochondrial membrane potential (MMP) and the expressions of Fas, FasL, Fadd and Caspase-8. Western blot was performed to analyze the expressions of Cyt-C, Pro-Caspase-9 and Pro-Caspase-3. Caspase activity kits were used to determine the activity of Caspase-9, Caspase-8 and Caspase-3. The results showed fucosterol could inhibit the growth of HL-60 cells, and the cell cycle was arrested at G2/M phase. HL-60 cells showed obvious apoptosis morphology. After being treated with fucosterol for 24 h, HL-60 cells decreased MMP, induced Cyt-C release and Caspase-9, Caspase-3 activation. Fucosterol also increased the protein expression of Fas, FasL, Fadd and Caspase-8. Moreover, the activity of Caspase-9, Caspase-8 and Caspase-3 was increased significantly. In conclusion, Fucosterol can induce HL-60 cells apoptosis, suggesting that it may be a potent agent for cancer prevention and treatment.

[734]

**TÍTULO / TITLE:** - Assessment of the topoisomerase I gene copy number as a predictive biomarker of objective response to irinotecan in metastatic colorectal cancer.

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

**REVISTA / JOURNAL:** - Scand J Gastroenterol. 2013 Nov 21.

●● [Enlace al texto completo \(gratis o de pago\) 3109/00365521.2013.856464](#)

**AUTORES / AUTHORS:** - Nygard SB; Christensen IJ; Nielsen SL; Nielsen HJ; Brunner N; Spindler KL

**INSTITUCIÓN / INSTITUTION:** - Section for Molecular Disease Biology, Department of Veterinary Disease Biology, Faculty of Health and Medical Sciences, University of Copenhagen, 49 Strandboulevarden, DK-2100 Copenhagen O, Denmark.

**RESUMEN / SUMMARY:** - Abstract Objective. DNA topoisomerase I is a putative biomarker of irinotecan efficacy with clinical associations previously demonstrated at the protein level. The purpose of the present study was to perform the first clinical investigation of the association between the DNA topoisomerase I gene (TOP1) copy number and objective response following irinotecan treatment in patients with metastatic colorectal cancer. Materials and methods. Formalin-fixed, paraffin-embedded tumor samples from 78 patients, who received irinotecan monotherapy in second line, were included. TOP1 was assessed by fluorescence in situ hybridization using a technically validated dual-probe combination that hybridizes to TOP1, located at 20q12-q13.1, and to the centromere region of chromosome 20 (CEN-20). In univariate logistic regression models, the TOP1 signal count per cell and the TOP1/CEN-20 ratio were associated with objective response, which was evaluated according to RECIST v.1.1. Results. Gain of TOP1 was identified in 52.6% and 37.2% using the following cutoff values: TOP1 signal count per cell  $\geq 3.6$  and TOP1/CEN-20  $\geq 1.5$ , respectively. A borderline significant association (Odds ratio (OR): 1.62;  $p = 0.07$ ) between a stepwise increase in the TOP1 signal count and objective response was demonstrated. In relation to the applied cutoff values, nonsignificant associations with objective response were identified for the TOP1 signal count (OR: 2.41;  $p = 0.23$ ) and for the TOP1/CEN-20 ratio (OR: 2.05;  $p = 0.30$ ). Conclusions. Despite limitations of the study the positive associations between TOP1 and objective response suggest that further analysis in larger tumor material, preferably in a randomized setting, is highly warranted.

[735]

**TÍTULO / TITLE:** - Comparative study of polymorphism frequencies of the CYP2D6, CYP3A5, CYP2C8 and IL-10 genes in Mexican and Spanish women with breast cancer.

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

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Oct;14(13):1583-92. doi: 10.2217/pgs.13.83.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.83](#)

**AUTORES / AUTHORS:** - Alcazar-Gonzalez GA; Calderon-Garciduenas AL; Garza-Rodriguez ML; Rubio-Hernandez G; Escorza-Trevino S; Olano-Martin E; Cerda-Flores RM; Castruita-Avila AL; Gonzalez-Guerrero JF; le Brun S; Simon-Buela L; Barrera-Saldana HA

**INSTITUCIÓN / INSTITUTION:** - Vitagenesis S.A. de C.V., Boulevard Puerta del Sol 1005, Colinas de San Jeronimo, Monterrey. N.L. C.P. 64630, Mexico.

**RESUMEN / SUMMARY:** - AIM: Pharmacogenetic studies in breast cancer (BC) may predict the efficacy of tamoxifen and the toxicity of paclitaxel and capecitabine. We determined the frequency of polymorphisms in the CYP2D6 gene associated with activation of tamoxifen, and those of the genes CYP2C8, CYP3A5 and DPYD associated with toxicity of paclitaxel and capecitabine. We also included a IL-10 gene polymorphism associated with advanced tumor stage at diagnosis. PATIENTS & METHODS: Genomic DNAs from 241 BC patients from northeast Mexico were genotyped using DNA microarray technology. RESULTS: For tamoxifen processing, CYP2D6 genotyping predicted that 90.8% of patients were normal metabolizers, 4.2% ultrarapid, 2.1% intermediate and 2.9% poor metabolizers. For paclitaxel and the CYP2C8 gene, 75.3% were normal, 23.4% intermediate and 1.3% poor metabolizers. Regarding the DPYD gene, only one patient was a poor metabolizer. For the IL-10 gene, 47.1% were poor metabolizers. CONCLUSION: These results contribute valuable information towards personalizing BC chemotherapy in Mexican women.

[736]

**TÍTULO / TITLE:** - Selective apoptosis of multiple myeloma cells in primary samples induced by arsenic trioxide.

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

**REVISTA / JOURNAL:** - Hematology. 2013 Oct 25.

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

[1179/1607845413Y.0000000134](#)

**AUTORES / AUTHORS:** - Rebersek K; Zontar DM; Cernelc P; Podgornik H

**RESUMEN / SUMMARY:** - OBJECTIVES: Currently, multiple myeloma (MM) is an incurable disease. Despite the fact that arsenic trioxide (ATO) shows promising results in vitro, data from treatment of patients with MM are disappointing. Due to these discrepancies, we compared the efficacy and selectivity of ATO at two different concentrations in samples from MM patients. METHODS: The extent of apoptosis induced by 2 and 5 microM ATO was evaluated by flow cytometry using annexin V. 34 diagnostic bone marrow samples obtained from MM patients were analysed. RESULTS: 5 microM ATO efficiently induced apoptosis in primary samples. Besides

efficacy, also selectivity of action on MM cells in comparison to remaining haematopoietic cells was demonstrated for 5 microM ATO but not for 2 microM ATO. DISCUSSION: Our study on primary samples confirmed that ATO has a potential role in therapeutic management of MM. Further controlled studies on MM patients are needed.

[737]

**TÍTULO / TITLE:** - An optimized five-gene multi-platform predictor of hormone receptor negative and triple negative breast cancer metastatic risk.

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

**REVISTA / JOURNAL:** - Breast Cancer Res. 2013 Oct 31;15(5):R103.

●● [Enlace al texto completo \(gratis o de pago\) 1186/bcr3567](#)

**AUTORES / AUTHORS:** - Yau C; Sninsky J; Kwok S; Wang A; Degnim A; Ingle JN; Gillett C; Tutt A; Waldman F; Moore D; Esserman L; Benz CC

**RESUMEN / SUMMARY:** - INTRODUCTION: Outcome predictors in use today are prognostic only for hormone receptor-positive (HRpos) breast cancer. Although microarray-derived multigene predictors of hormone receptor-negative (HRneg) and/or triple negative (Tneg) breast cancer recurrence risk are emerging, to date none have been transferred to clinically suitable assay platforms (for example, RT-PCR) or validated against formalin-fixed paraffin-embedded (FFPE) HRneg/Tneg samples. METHODS: Multiplexed RT-PCR was used to assay two microarray-derived HRneg/Tneg prognostic signatures (immune response signature with 7 genes (IR-7) and Buck-4) in a pooled FFPE collection of 139 chemotherapy-naive HRneg breast cancers. The prognostic value of the RT-PCR measured gene signatures were evaluated as continuous and dichotomous variables, and in conditional risk models incorporating clinical parameters. An optimized five-gene index was derived by evaluating gene combinations from both signatures. RESULTS: RT-PCR measured IR-7 and Buck-4 signatures proved prognostic as continuous variables; and conditional risk modeling chose nodal status, the IR-7 signature, and tumor grade as significant predictors of distant recurrence (DR). From the Buck-4 and IR-7 signatures, an optimized five-gene (TNFRSF17, CLIC5, HLA-F, CXCL13, XCL2) predictor was generated, referred to as the Integrated Cytokine Score (ICS) based on its functional pathway linkage through interferon-gamma and IL-10. Across all FFPE cases, the ICS was prognostic as either a continuous or dichotomous variable; and conditional risk modeling selected nodal status and ICS as DR predictors. Further dichotomization of node-negative/ICS-low FFPE cases identified a subset of low-grade HRneg tumors with <10% 5 year DR risk. The prognostic value of ICS was reaffirmed in 2 previously studied microarray assayed cohorts containing 274 node-negative and chemotherapy naive HRneg breast cancers, including 95 Tneg cases where it proved prognostically independent of Tneg molecular subtyping. In additional HRneg/Tneg microarray assayed cohorts, the five-gene ICS also proved prognostic irrespective of primary tumor nodal status and adjuvant chemotherapy intervention. CONCLUSION: We advanced the measurement of two previously reported microarray-derived HRneg/Tneg breast cancer prognostic signatures for use in FFPE samples, and derived an optimized five-gene Integrated Cytokine Score (ICS) with multi-platform capability of predicting metastatic outcome from primary HRneg/Tneg tumors independent of nodal status, adjuvant chemotherapy use, and Tneg molecular subtype.

[738]

**TÍTULO / TITLE:** - Silencing of survivin using YM155 induces apoptosis and chemosensitization in neuroblastomas cells.

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

**REVISTA / JOURNAL:** - Eur Rev Med Pharmacol Sci. 2013 Nov;17(21):2909-15.

**AUTORES / AUTHORS:** - Liang H; Zhang L; Xu R; Ju XL

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, Qilu Hospital, Shandong university, Jinan, P.R. China. [qlyyxl@126.com](mailto:qlyyxl@126.com)

**RESUMEN / SUMMARY:** - OBJECTIVES: Aggressive cell growth and chemoresistance are notorious obstacles in neuroblastoma therapy. Accumulating evidence suggests that survivin is preferentially expressed in cancer cells and plays a crucial role in cell division and apoptosis dysfunction. Thus, in the present study, we investigated whether silencing of survivin, using a novel small-molecule survivin suppressant, YM155 could suppress the proliferation and induce chemosensitization of neuroblastoma cells. MATERIALS AND METHODS: SH-SY5Y human neuroblastomas cells were treated with YM155 (10 to 500 mM) and/or chemotherapeutic agent cisplatin for 72 hours, and cell viability, apoptosis, mRNA and protein expression level were then evaluated. Furthermore, the efficacy of YM155 combined with cisplatin was further examined in established xenograft models. RESULTS: YM155 suppressed expression of survivin, inhibited the proliferation and induced apoptosis in SH-SY5Y cells in a concentration-dependent manner. Reduced levels of survivin sensitized SH-SY5Y to the chemotherapeutic agent cisplatin. YM155 showed antiproliferative effects and induced tumor regression and apoptosis in established SH-SY5Y xenograft models. Cisplatin showed antitumor activity against SH-SY5Y cells, it did not induce survivin upregulation. Combination treatment of YM155 and cisplatin induced a greater rate of apoptosis than the sum of the single-treatment rates and promoted tumor regression without enhanced body weight loss in the SH-SY5Y xenograft models. CONCLUSIONS: The concomitant combination of YM155 with cisplatin induced more intense apoptosis compared with each single treatment in vivo and in vitro. YM155 in combination with cisplatin is well tolerated and shows greater efficacy than either agent alone in mouse xenograft models.

[739]

**TÍTULO / TITLE:** - Resistant chronic myeloid leukemia beyond tyrosine-kinase inhibitor therapy: which role for omacetaxine?

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

**REVISTA / JOURNAL:** - Expert Opin Pharmacother. 2013 Oct 23.

●● Enlace al texto completo (gratis o de pago) [1517/14656566.2014.850491](https://doi.org/10.1186/1517-14656566.2014.850491)

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**RESUMEN / SUMMARY:** - The therapeutic armamentarium of chronic myeloid leukemia (CML) has been considerably improved after the introduction of first- and second-generation tyrosine-kinase inhibitors (TKIs). Accordingly, the natural history of the

diseases has changed, and patients in complete molecular response now have the same life expectancy of their healthy coetaneous. Notwithstanding these results, approximately 20 - 30% of patients do not respond optimally to TKIs therapy, and most of these patients are potential candidates to progress toward the accelerated or blastic phase of the disease. Unfortunately, patients who become resistant to both first- and second-generation TKIs develop BCR-ABL kinase domain mutations, against which TKIs have extremely low cross-activity. In particular, none of the TKIs, with the exception of ponatinib, has significant activity against T315 mutation, which is estimated to be present in approximately 15 - 20% of patients carrying BCR-ABL mutations. The use of omacetaxine mepesuccinate/homoharringtonine for the treatment of TKI-resistant CML patients regained interest due to its mechanism of action independent of binding to the ATP-binding pocket. Therefore, the activity of this compound is independent from the presence of BCR-ABL1 mutations, which makes it an attractive option for the treatment of CML patients after TKI failure.

[740]

**TÍTULO / TITLE:** - BH3 Profiling Discriminates Response to Cytarabine-Based Treatment of Acute Myelogenous Leukemia.

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

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0692](#)

**AUTORES / AUTHORS:** - Pierceall WE; Kornblau SM; Carlson NE; Huang X; Blake N; Lena R; Elashoff M; Konopleva M; Cardone MH; Andreeff M

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: 1Eutropics Pharmaceuticals, Cambridge, Massachusetts; 2Molecular Hematology and Therapy, Department of Stem Cell Transplantation; 3Division of Cancer Medicine, Department of Leukemia; and 4Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas.

**RESUMEN / SUMMARY:** - As acute myelogenous leukemia (AML) patient response to cytarabine-based standard-of-care treatment is variable, stratification into subgroups by biomarker-predicted response may lead to improved clinical outcomes. Here, we assess cell mitochondrial depolarization to proapoptotic signaling BH3-only peptides as a surrogate for the function of Bcl-2 family proteins to address clinical response to cytarabine-based therapy in patients with AML (N = 62). Peripheral blood mononuclear cell (PBMC) or bone marrow aspirate specimens were obtained from newly diagnosed patients with AML, viably preserved, and assayed by flow cytometry following BH3 profile assay with individual BH3 peptides. Mann-Whitney analysis indicates biomarker correlation with response to induction therapy: Notably, BIM priming was highly significant (P = 2 x 10<sup>-6</sup>) with a compelling sensitivity/specificity profile [area under curve (AUC) = 0.83; 95% confidence interval (CI), 0.73-0.94; P = 2 x 10<sup>-10</sup>]. Multivariate analysis indicates improved profiles for BIM readout + patient age (AUC = 0.89; 95% CI, 0.81-0.97) and BIM + patient age + cytogenetic status (AUC = 0.91; 95% CI, 0.83-0.98). When patients were stratified by cytogenetic status, BIM readout was significant for both intermediate (P = 0.0017; AUC = 0.88; 95% CI, 0.71-1.04) and unfavorable (P = 0.023; AUC = 0.79; 95% CI, 0.58-1.00) risk groups, demonstrating predictive power independent of cytogenetics. Additional analyses of secondary clinical

endpoints displayed correlation between overall survival ( $P = 0.037$ ) and event-free survival ( $P = 0.044$ ) when patients were stratified into tertiles by BIM peptide response. Taken together, these results highlight the potential utility of BH3 profiling in personalized diagnostics of AML by offering actionable information for patient management decisions. *Mol Cancer Ther*; 12(12); 1-10. ©2013 AACR.

[741]

**TÍTULO / TITLE:** - Lapatinib—induced NF-kappaB activation sensitizes triple-negative breast cancer cells to proteasome inhibitors.

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

**REVISTA / JOURNAL:** - *Breast Cancer Res.* 2013 Nov 12;15(6):R108.

●● [Enlace al texto completo \(gratis o de pago\) 1186/bcr3575](#)

**AUTORES / AUTHORS:** - Chen YJ; Yeh MH; Yu MC; Wei YL; Chen WS; Chen JY; Shih CY; Tu CY; Chen CH; Hsia TC; Chien PH; Liu SH; Yu YL; Huang WC

**RESUMEN / SUMMARY:** - INTRODUCTION: Triple-negative breast cancer (TNBC), a subtype of breast cancer with negative expressions of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2), is frequently diagnosed in younger women and has poor prognosis for disease-free and overall survival. Due to the lack of known oncogenic drivers for TNBC proliferation, clinical benefit from currently available targeted therapies is limited, and new therapeutic strategies are urgently needed. METHODS: Triple-negative breast cancer cell lines were treated with proteasome inhibitors in combination with lapatinib (a dual epidermal growth factor receptor (EGFR)/HER2 tyrosine kinase inhibitor). Their in vitro and in vivo viability was examined by MTT assay, clonogenic analysis, and orthotopic xenograft mice model. Luciferase reporter gene, immunoblot, and RT-qPCR, immunoprecipitation assays were used to investigate the molecular mechanisms of action. RESULTS: Our data showed that nuclear factor (NF)-kappaB activation was elicited by lapatinib, independent of EGFR/HER2 inhibition, in TNBCs. Lapatinib-induced constitutive activation of NF-kappaB involved Src family kinase (SFK)-dependent p65 and Ikbpp phosphorylations, and rendered these cells more vulnerable to NF-kappaB inhibition by p65 small hairpin RNA. Lapatinib but not other EGFR inhibitors synergized the anti-tumor activity of proteasome inhibitors both in vitro and in vivo. Our results suggest that treatment of TNBCs with lapatinib may enhance their oncogene addiction to NF-kappaB, and thus augment the anti-tumor activity of proteasome inhibitors. CONCLUSIONS: These findings suggest that combination therapy of a proteasome inhibitor with lapatinib may benefit TNBC patients.

[742]

**TÍTULO / TITLE:** - Indole diterpene alkaloids as novel inhibitors of the Wnt/beta-catenin pathway in breast cancer cells.

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

**REVISTA / JOURNAL:** - *Eur J Med Chem.* 2013 Oct 8;70C:594-606. doi: 10.1016/j.ejmech.2013.09.045.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ejmech.2013.09.045](#)

**AUTORES / AUTHORS:** - Sallam AA; Ayoub NM; Foudah AI; Gissendanner CR; Meyer SA; El Sayed KA

**INSTITUCIÓN / INSTITUTION:** - Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe, USA.

**RESUMEN / SUMMARY:** - Penitrems are indole diterpene alkaloids best known for their BK channel inhibition and tremorgenic effects in mammals. In a previous study, penitrems A-F (1-5), their biosynthetic precursors, paspaline (6) and emindole SB (7), and two brominated penitrem analogs 8 and 9 demonstrated promising in vitro antiproliferative, antimigratory, and anti-invasive effects in the MTT (MCF-7 and MDA-MB-231), wound-healing, and Cultrex® BME cell invasion (MDA-MB-231) assays, respectively. The study herein reports the novel ability of penitrem A to suppress total beta-catenin levels in MDA-MB-231 mammary cancer cells. Nine new penitrem analogs (10-18) were semisynthetically prepared, in an attempt to identify pharmacophores correlated with BK channel inhibition and tremorgenicity of penitrems and decrease their toxicity. The degree of BK channel inhibition was assessed using the nematode *Caenorhabditis elegans*, and in vivo tremorgenic EC50 was calculated using CD-1 male mice following an Up-and-Down Procedure (UDP). Although new analogs were generally less active than parent compound 1, some showed no BK channel inhibition or tremorgenicity and retained the ability of penitrem A (1) to suppress total beta-catenin levels in MDA-MB-231 cells. Paspaline (6) and emindole SB (7), both lacking BK channel inhibition and tremorgenicity, represent the simplest indole diterpene skeleton that retains the antiproliferative, antimigratory and total beta-catenin suppressing effects shown by the more complex penitrem A (1).

[743]

**TÍTULO / TITLE:** - The natural inhibitor of DNA topoisomerase I, camptothecin, modulates HIF-1alpha activity by changing miR expression patterns in human cancer cells.

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

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 19.

- [Enlace al texto completo \(gratis o de pago\) 1158/1535-7163.MCT-13-0729](#)

**AUTORES / AUTHORS:** - Bertozzi D; Marinello J; Manzo SG; Fornari F; Gramantieri L; Capranico G

**INSTITUCIÓN / INSTITUTION:** - 1Biochemistry, Bologna University.

**RESUMEN / SUMMARY:** - DNA Topoisomerase I inhibition by Camptothecin (CPT) derivatives can impair the hypoxia-induced cell transcriptional response. In the present work, we determined molecular aspects of the mechanism of CPT effects on HIF-1alpha activity in human cancer cells. In particular, we provide evidence that low concentrations of CPT, without interfering with HIF-1alpha mRNA levels, can reduce HIF-1alpha protein expression and activity. As luciferase assays demonstrated the involvement of the HIF-1alpha mRNA 3'UTR in CPT-induced impairment of HIF-1alpha protein regulation, we performed microarray analysis to identify CPT-induced modification of miRNAs targeting HIF-1alpha mRNA under hypoxic-mimetic conditions. The selected miRNAs were then further analyzed demonstrating a role for miR-17-5p and miR-155 in HIF-1alpha protein expression after CPT treatments. The present findings establish miRNAs as key factors in a molecular pathway connecting Top1 inhibition and human HIF-1alpha protein regulation and activity, widening the biological

and molecular activity of CPT derivatives and the perspective for novel clinical interventions.

[744]

**TÍTULO / TITLE:** - Sex hormones and breast cancer risk and prognosis.

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

**REVISTA / JOURNAL:** - Breast. 2013 Aug;22 Suppl 2:S38-43. doi: 10.1016/j.breast.2013.07.007.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.breast.2013.07.007](#)

**AUTORES / AUTHORS:** - Folkerd E; Dowsett M

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**RESUMEN / SUMMARY:** - The study of large prospective collections of plasma samples from women prior to the development of breast cancer has firmly established certain sex steroids as being significantly associated with risk. The strongest associations have been found in postmenopausal women in whom the within person variability of most hormones is markedly reduced but some positive associations have also been seen in premenopausal women. Plasma estrogens show the strongest correlations with risk and these are strengthened by measurement or calculation of the proportion of estradiol that circulates free of sex hormone binding globulin (SHBG), consistent with this being the most active fraction. The relationships have been reported to potentially explain virtually all of the association of breast cancer with body mass index in postmenopausal women; this is likely to be due to non-ovarian estrogen synthesis being prominent in subcutaneous fat. These strong relationships have led to plasma and urine estrogen levels being used as intermediate end-points in the search for genes that affect breast cancer risk via their role in steroid disposition. Plasma androgen levels also show a relationship with breast cancer risk that is weakened but not eliminated by 'correction' for estrogen levels. This has been argued to be evidence of the local production of estrogens being important in the etiology of breast cancer. Given that plasma steroid levels do not correlate closely with mammographic density, which is strongly associated with risk, the opportunity exists to combine the two factors in assessing breast cancer risk but the low availability of suitable estrogen assays is a major impediment to this. In established breast cancer, plasma estrogens have been found to correlate with gene expression of estrogen dependent genes and the expression of these varies across the menstrual cycle of premenopausal women. There is infrequently a need for routine measurement of plasma estrogen levels but it has been important in the comparative pharmacology and dose-related effectiveness of aromatase inhibitors. Measurement may be needed to identify residual ovarian function in women who have amenorrhea subsequent to cytotoxic chemotherapy indicating their unsuitability for aromatase inhibitor treatment. Use of highly sensitive assays has also revealed that the association between BMI and plasma estrogen levels persists in patients on 3<sup>rd</sup> generation aromatase inhibitors and that measurable increments in plasma estrogen levels occur with some vaginal estrogen preparations that are of concern in relation to treatment efficacy.

[745]

**TÍTULO / TITLE:** - Expression of Cell Cycle-Related Proteins, p16, p53 and p63 as Important Prognostic Markers in Gallbladder Adenocarcinoma.

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

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 Nov 1.

●● Enlace al texto completo (gratis o de pago) [1007/s12253-013-9710-5](#)

**AUTORES / AUTHORS:** - Kim K; Kim DH; Chae SW; Shin JH; Kim HJ; Do SI; Lee HJ; Koo JH; Pyo JS; Sohn JH

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108, Pyeong-dong, Jongro-gu, Seoul, 100-634, South Korea.

**RESUMEN / SUMMARY:** - Gallbladder cancer, the most common biliary tract malignancy, is a highly malignant neoplasm. In the present work, we have analyzed the significance of cell cycle-related proteins to predict prognosis and to provide guidance for optimal therapeutic decision-making in patients with gallbladder adenocarcinoma. The expressions of p16, p21, p27, p53, p63, cyclin D1, bcl-2 and bcl-6 were examined in a tissue microarray constructed from 96 cases of gallbladder adenocarcinoma by immunohistochemistry and correlated with clinicopathologic prognostic factors. Expression of p16 was correlated with a low pT stage, adenoma background and good prognosis. Cases with p63 expression showed a higher T stage, more frequent perineural invasion and poor prognosis when compared to cases without p63 expression. Over-expression of p53 or loss of p53 was associated with poor tumor differentiation, frequent distant metastasis and low disease-specific survival rate. The expressions of p21, p27, bcl-2, bcl-6 and cyclin D1 were not significant prognostic factors for gallbladder adenocarcinoma. These results indicate that p16, p63 and p53 can be used as prognostic markers in gallbladder adenocarcinoma; especially p53 and p63 as poor prognostic markers and p16 as a favorable prognostic marker.

[746]

**TÍTULO / TITLE:** - Synthesis, cytotoxicity and DNA binding of oxoazabenzodeanthracenes derivatives in colon cancer Caco-2 cells.

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

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 Nov;69:754-61. doi: 10.1016/j.ejmech.2013.08.038. Epub 2013 Sep 13.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.08.038](#)

**AUTORES / AUTHORS:** - Di Salvo A; Dugois P; Tandeo D; Peltekian M; Kong Thoo Lin P

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**RESUMEN / SUMMARY:** - New oxoazabenzodeanthracenes derivatives were synthesised and characterised. Their interactions with calf thymus DNA were studied by UV spectrophotometric analysis and a competitive ethidium bromide displacement assay. Cytotoxicity was determined by MTT assay, against colon adenocarcinoma (Caco-2 cells). Among all the oxoazabenzodeanthracenes derivatives reported herein only the piperidino derivative exhibited strong DNA binding properties and cytotoxic activity with IC50 values in the range of 16 +/- 1.5 µM (72-h treatment). In addition,

the piperidino derivative did not directly inhibit topoisomerase I and topoisomerase II enzymes. The results confirm that the presence of the oxoazabenz[de]anthracenes together with the piperidino functionality is crucial in exerting DNA binding and cytotoxic properties, hence demonstrating promise as a chemical scaffold for further development of new anticancer agents.

[747]

**TÍTULO / TITLE:** - Postmenopausal women with hormone receptor-positive breast cancer: balancing benefit and toxicity from aromatase inhibitors.

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

**REVISTA / JOURNAL:** - Breast. 2013 Aug;22 Suppl 2:S180-3. doi: 10.1016/j.breast.2013.07.035.

●● Enlace al texto completo (gratis o de pago) [1016/j.breast.2013.07.035](#)

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**RESUMEN / SUMMARY:** - Extensive clinical trial experience is available for aromatase inhibitors (AIs) in postmenopausal women upon which to evaluate the balance of potential benefit and toxicities. A meta-analysis revealed an advantage for AIs over tamoxifen in the monotherapy setting for recurrence but not breast cancer mortality, and an advantage in both of these parameters for switching to an AI after several years of tamoxifen. Importantly, no indication of a deleterious effect of AIs was identified in terms of death without recurrence in these meta-analyses. Regarding serious adverse events (AEs), there are data indicating an increase in cardiovascular AEs and bone fractures but a lower incidence of thromboembolic phenomena and endometrial cancer with AIs vis-a-vis tamoxifen. There does not appear to be a difference in cerebrovascular AEs. Musculoskeletal AEs are the most common clinically important AEs as they are the most common cause of discontinuation of therapy, which can have an adverse effect on outcomes. The balance of benefit and toxicity favors the use of AIs in the adjuvant setting but the absolute benefit from AIs can be decreased in patients with advancing age or increasing comorbidities.

[748]

**TÍTULO / TITLE:** - Optimizing tyrosine kinase inhibitor therapy in gastrointestinal stromal tumors: exploring the benefits of continuous kinase suppression.

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

**REVISTA / JOURNAL:** - Oncologist. 2013;18(11):1192-9. doi: 10.1634/theoncologist.2012-0361. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1634/theoncologist.2012-0361](#)

**AUTORES / AUTHORS:** - Le Cesne A; Blay JY; Reichardt P; Joensuu H

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Institut Gustave Roussy, Villejuif, France;

**RESUMEN / SUMMARY:** - The oral tyrosine kinase inhibitor (TKI) imatinib has revolutionized the treatment of gastrointestinal stromal tumors (GISTs), most of which harbor oncogenic mutation in genes that encode the receptor tyrosine kinases KIT or PDGFA. Imatinib is the standard of care for patients with advanced GIST and for

patients with primary GIST at significant risk of recurrence after surgery. Design. This review discusses data supporting continuous kinase suppression with imatinib and key issues, including response to imatinib reintroduction, effect of treatment interruption on secondary resistance to imatinib, and prognostic factors associated with sustained response to imatinib. Results. Long-term follow-up results of the B2222 study and updated results of the BFR14 trial demonstrate that continuous imatinib treatment in patients with advanced GIST is associated with reduced risk of progression. For patients progressing on or intolerant of imatinib, continuing therapy with TKIs sunitinib followed by regorafenib is recommended. In the adjuvant setting, final results of the trial by the Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie demonstrate that 3 years of adjuvant imatinib, compared with 1 year, significantly reduces the risk of recurrence and improves overall survival of patients with KIT-positive GIST at high risk of recurrence. Conclusions. Maintenance of therapy with TKIs is the key to successful treatment of GIST. Results from recent studies provide a strong rationale for continuous imatinib treatment for 3 years following surgical resection and long-term continuous administration in advanced or metastatic GIST.

[749]

**TÍTULO / TITLE:** - Tailored therapy in lung cancer.

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

**REVISTA / JOURNAL:** - Can Respir J. 2013 Sep-Oct;20(5):367-8.

**AUTORES / AUTHORS:** - Rakovich G; Tremblay L

**RESUMEN / SUMMARY:** - Historically, all non-small cell lung cancers were essentially grouped together and considered to be a single disease. However, it is now recognized that non-small cell lung cancer actually comprises a genetically diverse group of tumours. This, in turn, affords a new opportunity for the development of effective treatments tailored to individual tumours and patients. Advances in molecular biology have made possible the development of drugs against specific molecular targets on cancer cells, most notably the tyrosine kinase inhibitors. The relevant literature and current practice guidelines are discussed. In addition, other related areas of active investigation, including tumour vaccines and pharmacogenetics, are briefly reviewed.

[750]

**TÍTULO / TITLE:** - Arsenic disulfide-triggered apoptosis and erythroid differentiation in myelodysplastic syndrome and acute myeloid leukemia cell lines.

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

**REVISTA / JOURNAL:** - Hematology. 2013 Nov 4.

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

[1179/1607845413Y.0000000138](#)

**AUTORES / AUTHORS:** - Hu XM; Yuan B; Tanaka S; Song MM; Onda K; Tohyama K; Zhou AX; Toyoda H; Hirano T

**RESUMEN / SUMMARY:** - OBJECTIVES: Effects of arsenic disulfide (As<sub>2</sub>S<sub>2</sub>) were investigated by focusing on growth inhibition, apoptosis induction, and erythroid differentiation in MDS-L, F-36p and HL-60 cells, derived from myelodysplastic syndrome (MDS), MDS/acute myeloid leukemia (AML), and de novo AML, respectively.

**METHODS:** Cell viability was determined by MTT assay. Apoptosis induction was analyzed using Annexin V/propidium iodide staining. Erythroid differentiation was assessed by the expression level of CD235a, a marker for detection of the erythroid cell lineage. The activation of p38 MAPK and the expression profile of apoptosis-related proteins Bcl-2 and Bid were analyzed using western blot. **RESULTS:** As2S2 inhibited cell growth of these cell lines. Of note, the IC50 value of As2S2 in MDS-L cells was comparable to that in F-36p cells, and was half of that in HL-60 cells. A dose-dependent decrease in cell viability and concomitant increase in the percentage of apoptotic cells were observed in F-36p cells treated with 8 and 16 microM As2S2 for 72 hours. However, similar phenomena were only observed in HL-60 cells when treated with as high as 16 microM As2S2. Furthermore, As2S2 exerted more potent erythroid differentiation-inducing activity on F-36p cells than HL-60 cells. Interestingly, negative correlation between p38 MAPK signaling pathway and As2S2-induced erythroid differentiation was observed in HL-60 cells. Treatment with relatively high concentration of As2S2 resulted in the downregulation of Bcl-2 and Bid proteins in HL-60 cells. **DISCUSSION:** These results suggest that compared to AML cell line, MDS and MDS/AML cell lines are more sensitive to not only the erythroid differentiation-inducing activity of As2S2, but also its cytotoxicity associated with apoptosis induction. These findings further provide novel insight into As2S2 action toward its use for clinical application in patients with hematological disorders.

[751]

**TÍTULO / TITLE:** - Minor Antigen Distribution Predicts Site-Specific Graft-versus-Tumor Activity of Adoptively Transferred, Minor Antigen-Specific CD8 T Cells.

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

**REVISTA / JOURNAL:** - Biol Blood Marrow Transplant. 2013 Oct 17. pii: S1083-8791(13)00457-6. doi: 10.1016/j.bbmt.2013.10.009.

•• Enlace al texto completo (gratis o de pago) [1016/j.bbmt.2013.10.009](http://1016/j.bbmt.2013.10.009)

**AUTORES / AUTHORS:** - Shand JC; Qin H; Nasholm N; Capitini CM; Fry TJ

**INSTITUCIÓN / INSTITUTION:** - Blood and Marrow Transplant Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. Electronic address:

[Jessica\\_Shand@URMC.Rochester.edu](mailto:Jessica_Shand@URMC.Rochester.edu).

**RESUMEN / SUMMARY:** - The clinical success of allogeneic T cell therapy for cancer relies on the selection of antigens that can effectively elicit antitumor responses with minimal toxicity toward nonmalignant tissues. Although minor histocompatibility antigens (MiHA) represent promising targets, broad expression of these antigens has been associated with poor responses and T cell dysfunction that may not be prevented by targeting MiHA with limited expression. In this study, we hypothesized that antitumor activity of MiHA-specific CD8 T cells after allogeneic bone marrow transplantation (BMT) is determined by the distribution of antigen relative to the site of tumor growth. To test this hypothesis, we utilized the clinically relevant male-specific antigen HY and studied the fate of adoptively transferred, HY-CD8+ T cells (HY-CD8) against a HY-expressing epithelial tumor (MB49) and pre-B cell leukemia (HY-E2APBX ALL) in BMT recipients. Transplants were designed to produce broad HY expression in nonhematopoietic tissues (female --> male BMT, [F-->M]), restricted HY expression in hematopoietic tissues (male --> female BMT, [M-->F]) tissues, and no HY tissue

expression (female --> female BMT, [F-->F]). Broad HY expression induced poor responses to MB49 despite sublethal graft-versus-host disease and accumulation of HY-CD8 in secondary lymphoid tissues. Antileukemia responses, however, were preserved. In contrast, restriction of HY expression to hematopoietic tissues restored MB49 responses but resulted in a loss of antileukemia responses. We concluded that target alloantigen expression in the same compartment of tumor growth impairs CD8 responses to both solid and hematologic tumors.

[752]

**TÍTULO / TITLE:** - A prognostic test to predict the risk of metastasis in uveal melanoma based on a 15-gene expression profile.

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

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1102:427-40. doi: 10.1007/978-1-62703-727-3\_22.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-727-3\\_22](#)

**AUTORES / AUTHORS:** - Harbour JW

**INSTITUCIÓN / INSTITUTION:** - Bascom Palmer Eye Institute, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA.

**RESUMEN / SUMMARY:** - Uveal (ocular) melanoma is an aggressive cancer that metastasizes in up to half of patients. Uveal melanoma spreads preferentially to the liver, and the metastatic disease is almost always fatal. There are no effective therapies for advanced metastatic disease, so the most promising strategy for improving survival is to detect metastasis at an earlier stage or to treat high-risk patients in an adjuvant setting. An accurate test for identifying high-risk patients would allow for such personalized management as well as for stratification of high-risk patients into clinical trials of adjuvant therapy. We developed a gene expression profile (GEP) that distinguishes between primary uveal melanomas that have a low metastatic risk (class 1 tumors) and those with a high metastatic risk (class 2 tumors). We migrated the GEP from a high-density microarray platform to a 15-gene, qPCR-based assay that is now performed in a College of American Pathologists (CAP)-accredited Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory on a routine clinical basis on very small samples obtained by fine needle aspiration and on archival formalin-fixed specimens. We collaborated with several centers to show that our specimen collection protocol was easily learned and performed and that it allowed samples to be safely and reliably transported from distant locations with a very low failure rate. Finally, we showed in a multicenter, prospective study that our GEP assay is highly accurate for predicting which patients will develop metastatic disease, and it was significantly superior to the previous gold standard, chromosome 3 testing for monosomy 3. This is the only prognostic test in uveal melanoma ever to undergo such extensive validation, and it is currently being used in a commercial format under the trade name DecisionDx-UM in over 100 centers in the USA and Canada.

[753]

**TÍTULO / TITLE:** - Changes in ER, PR and HER2 receptors status after neoadjuvant chemotherapy in breast cancer.

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

**REVISTA / JOURNAL:** - Pathol Res Pract. 2013 Dec;209(12):797-802. doi: 10.1016/j.prp.2013.08.012. Epub 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1016/j.prp.2013.08.012](https://doi.org/10.1016/j.prp.2013.08.012)

**AUTORES / AUTHORS:** - Yang YF; Liao YY; Li LQ; Xie SR; Xie YF; Peng NF

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, The Affiliated Dongguan Shilong People's Hospital of Southern Medical University, Dongguan, Guangdong Province, China.

**RESUMEN / SUMMARY:** - Previous studies have reported conflicting results regarding the impact of neoadjuvant chemotherapy (NAC) on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status in breast cancer. Our aim was to investigate whether NAC induces some selective change in the breast biomarkers. We retrospectively detected the immunohistochemical results of ER, PR and HER2 between the core biopsy and surgical excision specimens in 113 patients with NAC. As a control group, we analyzed sample pairs from 102 patients without NAC. Fourteen (12.4%) of 113 patients undergoing NAC showed the ER status modulation in the surgically removed specimen as compared with only 4 (3.9%) of 102 women without NAC ( $p=0.025$ ). Eighteen (15.9%) of 113 patients given NAC appeared in the PR status alteration in the final surgical specimen, whereas only 7 (6.9%) of 102 patients without NAC did ( $p=0.038$ ). The HER2 status shift was found in 17 (15.0%) of 113 patients with NAC and in 6 (5.9%) of 102 patients without NAC, respectively ( $p=0.030$ ). Neoadjuvant chemotherapy does change ER, PR and HER2 status in a statistically significant manner. Retesting these biomarkers of the residual tumor should be considered to improve future tailored adjuvant therapies.

[754]

**TÍTULO / TITLE:** - Functional Annotation of Differentially Regulated Gene Set Using WebGestalt: A Gene Set Predictive of Response to Ipilimumab in Tumor Biopsies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1101:31-42. doi: 10.1007/978-1-62703-721-1\_3.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-721-1\\_3](https://doi.org/10.1007/978-1-62703-721-1_3)

**AUTORES / AUTHORS:** - Kirov S; Ji R; Wang J; Zhang B

**INSTITUCIÓN / INSTITUTION:** - Applied Genomics, Bristol Myers-Squibb, Pennington, NJ, USA.

**RESUMEN / SUMMARY:** - Most high-throughput methods which are used in molecular biology generate gene lists. Interpreting large gene lists can reveal mechanistic insights and generate useful testable hypotheses. The process can be cumbersome and challenging. Multiple commercial and open solution currently exist that can aid researchers in the functional annotation of gene lists. The process of gene set annotation includes dataset preparation, which is method specific, gene list annotation and analysis and interpretation of the significant associations that were found. In this chapter, we demonstrate how WebGestalt can be applied to gene lists generated from transcriptional profiling data.

[755]

**TÍTULO / TITLE:** - B7-H6 Protein Expression has no Prognostic Significance in Human Gastric Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 Nov 16.

●● Enlace al texto completo (gratis o de pago) [1007/s12253-013-9686-1](#)

**AUTORES / AUTHORS:** - Chen XJ; Shen J; Zhang GB; Chen WC

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, The First Affiliated Hospital of Soochow University, Suzhou, 215006, China.

**RESUMEN / SUMMARY:** - B7-H6, a novel member of the B7 family which binds to NKp30 to trigger antitumor NK cell cytotoxicity and cytokine secretion. Recently, B7-H family has been reported to be a negative regulator of the immune response in patients with gastric carcinoma. However, no reports have investigated the clinical significance of B7-H6 expression in human gastric cancer. We present the first study to the clinicopathological and prognostic value of B7-H6 in primary gastric tumors and adjacent non-tumor tissues at the protein level. Here we show that B7-H6 immunoreactivity was expressed in 6/60 (10 %) gastric tumors and 8/43 (18.60 %) adjacent non-tumor tissues. No statistical difference was found between B7-H6 expression and various prognostic factors; however, B7-H6-positive carcinomas were significantly associated with a higher differentiation ( $p = 0.047$ ). The survival analysis did not confirm the prognostic significance of B7-H6 expression in gastric cancer patients. Our data suggest that B7-H6, as detected by immunohistochemistry, is of limited value as a prognostic marker for gastric cancer.

[756]

**TÍTULO / TITLE:** - Expression of molecular markers associated with the mammalian target of rapamycin pathway in nonmetastatic renal cell carcinoma: Effect on prognostic outcomes following radical nephrectomy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Urol Oncol. 2013 Nov 13. pii: S1078-1439(13)00305-0. doi: 10.1016/j.urolonc.2013.07.014.

●● Enlace al texto completo (gratis o de pago) [1016/j.urolonc.2013.07.014](#)

**AUTORES / AUTHORS:** - Nishikawa M; Miyake H; Harada KI; Fujisawa M

**INSTITUCIÓN / INSTITUTION:** - Division of Urology, Kobe University Graduate School of Medicine, Kobe, Japan.

**RESUMEN / SUMMARY:** - OBJECTIVES: To evaluate the expression of multiple molecular markers involved in mammalian target of rapamycin (mTOR) signaling pathway in renal cell carcinoma (RCC) to determine the prognostic significance of these markers following radical nephrectomy. MATERIAL AND METHODS: The expression levels of 5 markers, including PTEN, phosphorylated (p)-Akt, p-mTOR, p-p70 ribosomal S6 kinase, and p-4E-binding protein 1 (4E-BP1), were measured in radical nephrectomy specimens from 137 patients with nonmetastatic RCC by immunohistochemical staining. RESULTS: During the follow-up period of this series (median, 63.5 mo), disease recurrence occurred in 59 of the 137 patients (43.0%), with a 5-year recurrence-free survival rate of 58.3%. On Univariate analysis, expression levels of p-mTOR and p-4E-BP1, in addition to the C-reactive protein level, pathological stage, and microvascular invasion, were identified as significant predictors for disease recurrence. Of these factors, the expression of p-4E-BP1, C-reactive protein level, and

pathological T stage appeared to be independently related to recurrence-free survival on multivariate analysis. Moreover, significant differences were observed in recurrence-free survival according to the positive numbers of these 3 independent factors; that is, disease recurrence developed in 5 of 42 patients with negative results for any risk factor (11.9%), 23 of 50 patients with positive results for a single risk factor (46.0%), and 31 of 45 patients with positive results for 2 or 3 risk factors (68.8%).

**CONCLUSIONS:** The combined evaluation of the expression levels of potential markers in the mTOR signaling pathway, particularly p-4E-BP1, in RCC specimens with conventional prognostic parameters would contribute to the accurate prediction of disease recurrence following radical nephrectomy for nonmetastatic RCC.

[757]

**TÍTULO / TITLE:** - Yhhu3813 is a novel selective inhibitor of c-Met Kinase that inhibits c-Met-dependent neoplastic phenotypes of human cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Pharmacol Sin. 2013 Nov 18. doi: 10.1038/aps.2013.125.

●● Enlace al texto completo (gratis o de pago) [1038/aps.2013.125](#)

**AUTORES / AUTHORS:** - He CX; Ai J; Xing WQ; Chen Y; Zhang HT; Huang M; Hu YH; Ding J; Geng MY

**INSTITUCIÓN / INSTITUTION:** - Division of Anti-tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.

**RESUMEN / SUMMARY:** - Aim:c-Met kinase deregulation is strongly associated with the formation, progression and dissemination of human cancers. In this study we identified Yhhu3813 as a small-molecule inhibitor of c-Met kinase and characterized its antitumor properties both in vitro and in vivo. Methods:The activities of different kinases were measured using ELISA assays and signaling proteins in the cells were detected with Western blotting. Cell proliferation was assessed using SRB or MTT assay in twenty human cell lines and cell cycle distribution was determined with flow cytometry. Transwell-based assay was used to evaluate cell migration and invasion. Cell invasive growth was detected by a morphogenesis assay. c-Met overactivated human NSCLC cell line EBC-1 xenografts were used to evaluate the in vivo anti-tumor efficacy. Results:Yhhu3813 potently inhibited c-Met kinase activity in vitro with an IC50 value of 2.4±0.3 nmol/L, >400-fold higher than that for a panel of 15 different tyrosine kinases, suggesting a high selectivity of Yhhu3813. The compound (20, 100 and 500 nmol/L) dose-dependently inhibited the phosphorylation of c-Met and its key downstream Akt and Erk signal cascades in multiple c-Met aberrant human cancer cell lines, regardless of the mechanistic complexity in c-Met activation across different cellular contexts. In 20 human cancer cell lines harboring different backgrounds of c-Met expression/activation, Yhhu3813 potently inhibited c-Met-driven cell proliferation via arresting cells at G1/S phase. Furthermore, Yhhu3813 substantially impaired c-Met-mediated cell migration, invasion, scattering, and invasive growth. Oral administration of EBC-1 xenograft mice with Yhhu3813 (50 or 100 mg.kg<sup>-1</sup>.d<sup>-1</sup>, qd, for 2 weeks) dose-dependently suppressed the tumor growth, which was correlated with a reduction in the intratumoral proliferation index and c-Met signaling. Conclusion:Yhhu3813 is a potent selective inhibitor of c-Met that inhibits c-Met-dependent neoplastic phenotypes of human cancer cells in vitro and in vivo.

[758]

**TÍTULO / TITLE:** - Polyphenol extract of *Phyllanthus emblica* (PEEP) induces inhibition of cell proliferation and triggers apoptosis in cervical cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Res. 2013 Nov 19;18:46. doi: 10.1186/2047-783X-18-46.

●● Enlace al texto completo (gratis o de pago) [1186/2047-783X-18-46](#)

**AUTORES / AUTHORS:** - Zhu X; Wang J; Ou Y; Han W; Li H

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**RESUMEN / SUMMARY:** - BACKGROUND: The aim of this study is to investigate the effects of polyphenol extract from *Phyllanthus emblica* (PEEP) on cervical cancer cells and to explore the underlying mechanism. METHODS: MTT assay was used to measure inhibition of proliferation of cervical cancer (HeLa) cells after treatment with PEEP at concentrations of 0, 50, 100, 150, and 200 mg/ml for 48 hours. HeLa cells were treated with PEEP (150 mg/ml) for 48 hours in the following analysis. Karyomorphism was assessed by immunofluorescence using DAPI staining, and cell apoptosis and cell cycle were assessed using flow cytometry. Three apoptotic marker proteins, namely, Fas, FasL, and cleaved caspase-8, were assessed by western blotting. RESULTS: PEEP inhibited the growth of HeLa cells, and the optimum concentration of PEEP was 150 mg/ml. In addition, the karyomorphism of HeLa cells after treatment with PEEP was abnormal. Furthermore, PEEP induced arrest of the HeLa cell cycle at G2/M phase, and triggered apoptosis. PEEP also induced significant Fas and FasL activation, and cleavage of caspase-8. CONCLUSIONS: Our study indicates that PEEP is effective in inhibiting HeLa cell proliferation by inducing cell cycle arrest at G2/M phase and inducing apoptosis.

[759]

**TÍTULO / TITLE:** - Redirecting Apoptosis to Aponecrosis Induces Selective Cytotoxicity to Pancreatic Cancer Cells through Increased ROS, Decline in ATP Levels, and VDAC.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 19.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-](#)

[0234](#)

**AUTORES / AUTHORS:** - Dinnen RD; Mao Y; Qiu W; Cassai N; Slavkovich VN; Nichols G; Su GH; Brandt-Rauf P; Fine RL

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: 1Experimental Therapeutics Program, Division of Medical Oncology, The Pancreas Center at Columbia; 2Department Pathology and Otolaryngology, Herbert Irving Cancer Center, Columbia University, College of Physicians and Surgeons; 3Department of Pathology and Laboratory Medicine, Harbor VA Medical Center, SUNY Downstate Medical Center, Brooklyn, New York; 4Department Environmental Health Science, Columbia University, New York; and 5University of Illinois School of Public Health, University of Illinois, Chicago, Illinois.

**RESUMEN / SUMMARY:** - Pancreatic cancer cell lines with mutated ras underwent an alternative form of cell death (aponecrosis) when treated concomitantly with clinically achievable concentrations of arsenic trioxide, ascorbic acid, and disulfiram (Antabuse; AAA). AAA's major effects are mediated through generation of intracellular reactive oxygen species (ROS) and more than 50% decline in intracellular ATP. N-acetyl cysteine and a superoxide dismutase mimetic prevented aponecrosis and restored intracellular ATP levels. DIDS (4,4'-diisothiocyanatostilbene-2, 2' disulfonic acid), the pan- Voltage-Dependent Anion Channel (VDAC), -1, 2, 3 inhibitor and short hairpin RNA (shRNA) to VDAC-1 blocked cell death and ROS accumulation. In vivo exposure of AAA led to a 62% reduction in mean tumor size and eliminated tumors in 30% of nude mice with PANC-1 xenografts. We concluded that early caspase-independent apoptosis was shifted to VDAC-mediated "targeted" aponecrosis by the addition of disulfiram to arsenic trioxide and ascorbic acid. Conceptually, this work represents a paradigm shift where switching from apoptosis to aponecrosis death pathways, also known as targeted aponecrosis, could be utilized to selectively kill pancreatic cancer cells resistant to apoptosis. Mol Cancer Ther; 12(12); 1-12. ©2013 AACR.

[760]

**TÍTULO / TITLE:** - Kinase inhibitors and immune check-point blockade for the treatment of metastatic melanoma and advanced cancer: synergistic or antagonistic?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Pharmacother. 2013 Dec;14(18):2457-62. doi: 10.1517/14656566.2013.849244. Epub 2013 Oct 21.

●● Enlace al texto completo (gratis o de pago) [1517/14656566.2013.849244](https://doi.org/10.1517/14656566.2013.849244)

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**RESUMEN / SUMMARY:** - In recent years, therapeutic approaches for many tumors have broadened or even shifted entirely from cytotoxic chemotherapy to specific targeting of dysregulated proteins (predominately kinases), and more recently, harnessing of the anti-tumor immune response. The most prominent example of this shift is the management of metastatic melanoma, where BRAF and MEK inhibition and CLTA-4 blockade have established an entirely new standard of care in the last 3 years. Targeted kinase inhibition and immune checkpoint blockade have different strengths and weaknesses. Kinase inhibitors generally have rapid and impressive response rates but modest progression-free survival while immunotherapy can achieve durable tumor control, but is often associated with lower response rates and slower time to clinical benefit. These approaches would seem to be complementary however the results of early combination studies suggest that caution is advised when combining targeted kinase inhibition with immunotherapy. In this context, rigorous biomarker driven clinical trials are needed to further elucidate mechanisms of both benefit and toxicity. Depending on disease specific biology, it seems likely that both combination and sequential approaches of kinase inhibitors with immunotherapy will be required in order to harness the full potential of these approaches.

[761]

**TÍTULO / TITLE:** - Expression of cell cycle and apoptosis-related proteins in ameloblastoma and keratocystic odontogenic tumor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Diagn Pathol. 2013 Dec;17(6):518-21. doi: 10.1016/j.anndiagpath.2013.06.006. Epub 2013 Oct 1.

●● Enlace al texto completo (gratis o de pago)

[1016/j.anndiagpath.2013.06.006](#)

**AUTORES / AUTHORS:** - Metgud R; Gupta K

**INSTITUCIÓN / INSTITUTION:** - Department of Oral and Maxillofacial Pathology, Pacific Dental College and Hospital, PAHER University, Udaipur, Rajasthan, India. Electronic address: [rashmi\\_metgud@rediffmail.com](mailto:rashmi_metgud@rediffmail.com).

**RESUMEN / SUMMARY:** - Tumors arising from epithelium of the odontogenic apparatus or from its derivatives or remnants exhibit considerable histologic variation and are classified into several benign and malignant entities. A high proliferative activity of the odontogenic epithelium in ameloblastoma (AM) and keratocystic odontogenic tumor (KCOT) has been demonstrated in some studies individually. However, very few previous studies have simultaneously evaluated cell proliferation and apoptotic indexes in AM and KCOT, comparing both lesions. The aim of this study was to assess and compare cell proliferation and apoptotic rates between these two tumors. Specimens of 15 solid AM and 15 KCOT were evaluated. The proliferation index (PI) was assessed by immunohistochemical detection of Ki-67 and the apoptotic index (AI) by methyl green-pyronin stain. KCOT presented a higher PI than AM ( $P < .05$ ). No statistically significant difference was found in the AI between AM and KCOT. PI and AI were higher in the peripheral cells of AM and respectively in the suprabasal and superficial layers of KCOT. In conclusion, KCOT showed a higher cell proliferation than AM and the AI was similar between these tumors. These findings reinforce the classification of KCOT as an odontogenic tumor and should contribute to its aggressive clinical behavior.

[762]

**TÍTULO / TITLE:** - Proteomic analysis reveals tanshinone IIA enhances apoptosis of advanced cervix carcinoma CaSki cells through mitochondria intrinsic and endoplasmic reticulum stress pathways.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proteomics. 2013 Oct 24. doi: 10.1002/pmic.201300274.

●● Enlace al texto completo (gratis o de pago) [1002/pmic.201300274](#)

**AUTORES / AUTHORS:** - Pan TL; Wang PW; Hung YC; Huang CH; Rau KM

**INSTITUCIÓN / INSTITUTION:** - School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan; Chinese Herbal Medicine Research Team, Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan.

**RESUMEN / SUMMARY:** - Cervix cancer is the second most common cancer among women worldwide, whereas paclitaxel, the first line chemotherapeutic drug used to treat cervical cancer, shows low chemosensitivity on the advanced cervical cancer cell line. Tanshinone IIA (Tan IIA) exhibited strong growth inhibitory effect on CaSki cells ( $IC_{50} = 5.51 \mu M$ ) through promoting caspase cascades with concomitant

upregulating the phosphorylation of p38 and JNK signaling. Comprehensive proteomics revealed the global protein changes and the network analysis implied that Tan IIA treatment would activate ER stress pathways that finally lead to apoptotic cell death. Moreover, ER stress inhibitor could alleviate Tan IIA caused cell growth inhibition and ameliorate C/EBP-homologous protein as well as apoptosis signal-regulating kinase 1 mediated cell death. The therapeutic interventions targeting the mitochondrial-related apoptosis and ER stress responses might be promising strategies to conquer paclitaxel resistance.

[763]

**TÍTULO / TITLE:** - Continuous low-dose irradiation by I-125 seeds induces apoptosis of gastric cancer cells regardless of histological origin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Oct 22;15(1).

**AUTORES / AUTHORS:** - Takabayashi K; Kashiwagi K; Kawata T; Sato T; Matsuoka K; Hisamatsu T; Takaishi H; Hibi T; Ogata H; Yahagi N; Kitagawa Y; Shigematsu N; Kanai T

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology and Hepatology; Department of Internal Medicine; School of Medicine; Keio University; Tokyo, Japan.

**RESUMEN / SUMMARY:** - The efficacy of conventional radiation therapy for gastric cancer is controversial. In this study, we evaluated the in vitro and in vivo effects of continuous low-dose-rate irradiation by I-125 seeds on different histological types of gastric cancer cell lines. Three human gastric cancer cell lines (MKN74, MKN45, and NUGC4) were treated with or without continuous low-dose irradiation by I-125 seeds in vitro and in vivo. Cell viability, apoptosis, caspase-3 assay, and cell-cycle distribution were examined in vitro. Body weight and tumor volumes of BALB/c nude mice bearing MKN74, MKN45, and NUGC4 gastric cancer xenografts were measured, and in vivo cell proliferation and apoptosis assays were performed by Ki67 and TUNEL staining, respectively. Continuous low-dose-rate irradiation by I-125 seeds reduced cell viability and induced cell apoptosis through the activation of caspase-3, and led to the accumulation of cells in the G<sub>2</sub>/M phase in vitro. It also suppressed the growth of gastric cancer xenografts in nude mice, while inhibiting cell proliferation and inducing apoptosis as demonstrated by Ki67 and TUNEL staining. Therefore, our data suggest that continuous low-dose-rate irradiation by I-125 seeds could be a promising new option for gastric cancer treatment, regardless of histological origin.

[764]

**TÍTULO / TITLE:** - Single-agent obatoclox (GX15-070) potently induces apoptosis and pro-survival autophagy in head and neck squamous cell carcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Oncol. 2013 Nov 8. pii: S1368-8375(13)00722-7. doi: 10.1016/j.oraloncology.2013.10.013.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1016/j.oraloncology.2013.10.013](#)

**AUTORES / AUTHORS:** - Yazbeck VY; Li C; Grandis JR; Zang Y; Johnson DE

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, University of Pittsburgh, University of Pittsburgh Cancer Institute, Pittsburgh, PA, United States.

**RESUMEN / SUMMARY:** - OBJECTIVES: More than half of head and neck squamous cell carcinoma (HNSCC) patients are initially treated with curative intent, but will relapse over the course of their disease and have poor prognosis with a median survival of approximately 6 months. Novel therapeutic approaches are in desperate need for this patient population. The anti-apoptotic BCL-2 family proteins such as BCL-2, BCL-XL, and MCL-1 are involved in oncogenesis and chemoresistance and are overexpressed in HNSCC. Obatoclax is a small-molecule antagonist of the BH3-binding groove of anti-apoptotic BCL-2 family. We evaluated the activity of obatoclax against 4 HNSCC cell lines (UMSCC-1, Cal33, 1483, UMSCC-22A). METHODS: Cell viability was determined by MTT assay, cell cycle status by propidium iodide staining, and apoptosis by Annexin-V staining and immunoblotting. Autophagy was assessed by immunofluorescence and immunoblotting. RESULTS: All four HNSCC cell lines were highly sensitive to single-agent obatoclax with IC<sub>50</sub>'s ranging from 46 to 177 nM. Obatoclax induced apoptosis in all four HNSCC cell lines as evidenced by increases in sub-G1 DNA content, Annexin-V staining, and PARP cleavage. In addition, obatoclax induced autophagy in all 4 cell lines, and the addition of the autophagy inhibitor chloroquine enhanced obatoclax cytotoxicity. CONCLUSION: Our findings demonstrate potent monotherapeutic activity of obatoclax against HNSCC cells, and enhancement of this activity in the presence of chloroquine. This preclinical study suggests that obatoclax might have therapeutic value in the treatment of HNSCC, either alone or in combination with inhibitors of autophagy.

[765]

**TÍTULO / TITLE:** - Esters and amides of maslinic acid trigger apoptosis in human tumor cells and alter their mode of action with respect to the substitution pattern at C-28.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 Oct 12;70C:259-272. doi: 10.1016/j.ejmech.2013.10.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.10.016](#)

**AUTORES / AUTHORS:** - Siewert B; Pianowski E; Csuk R

**INSTITUCIÓN / INSTITUTION:** - Bereich Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Strasse 2, D-06120 Halle (Saale), Germany.

**RESUMEN / SUMMARY:** - Cancer is one of the most commonly diagnosed diseases worldwide; its mortality rate is high, and there is still a demand for the development of antitumor active drugs. Triterpenic acids show many pharmacological effects, among them antitumor activity. One of these, maslinic acid-1 is of interest because of its antitumor profile. It is not only cytotoxic but also triggers apoptosis in various human tumor cell lines. To improve the cytotoxicity of parent 1 we set out to synthesize a series of esters and amides differing in structure and lipophilicity. These compounds were tested in a sulforhodamine B assay for cytotoxicity, and screened for their ability to induce apoptosis using an acridine orange/propidium iodide assay, DNA laddering and cell cycle experiments. Esters containing small-chain, lipophilic residues increased the cytotoxicity whereas amides as well long-chain esters led to a decrease in activity. The antitumor activity seems to be independent from the substitution pattern at position C-28 for esters and amides but alters their mode of action.

[766]

**TÍTULO / TITLE:** - Small-molecule IAP antagonists sensitize cancer cells to TRAIL-induced apoptosis: Roles of XIAP and cIAPs.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 5.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0153](#)

**AUTORES / AUTHORS:** - Finlay D; Vamos M; Gonzalez-Lopez M; Ardecky RJ; Reddy Ganji S; Yuan H; Su Y; Cooley TR; Hauser CT; Welsh K; Reed JC; Cosford ND; Vuori K

**INSTITUCIÓN / INSTITUTION:** - 1Cancer Center, Sanford-Burnham Medical Research Institute.

**RESUMEN / SUMMARY:** - Tumor Necrosis Factor Related Apoptosis Inducing Ligand (TRAIL) is a promising anti-cancer agent because it shows apoptosis-inducing activity in transformed, but not in normal cells. As with most anti-cancer agents, however, its clinical use is restricted by either inherent or acquired resistance by cancer cells. We demonstrate here that small-molecule SMAC mimetics that antagonize the Inhibitor of Apoptosis Proteins (IAPs) potently sensitize previously resistant human cancer cell lines, but not normal cells, to TRAIL-induced apoptosis, and that they do so in a caspase-8-dependent manner. We further show that the compounds have no cytotoxicity as single agents. Also, we demonstrate that several IAP family members likely participate in the modulation of cellular sensitivity to TRAIL. Finally, we note that the compounds that sensitize cancer cells to TRAIL are the most efficacious in binding to XIAP, and in inducing cIAP-1 and cIAP-2 degradation. Our studies thus describe valuable compounds that allow elucidation of the signaling events occurring in TRAIL resistance, and demonstrate that these agents act as potent TRAIL-sensitizing agents in a variety of cancer cell lines.

[767]

**TÍTULO / TITLE:** - Punicalagin induces apoptotic and autophagic cell death in human U87MG glioma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Pharmacol Sin. 2013 Nov 5;34(11):1411-9. doi: 10.1038/aps.2013.98. Epub 2013 Sep 30.

●● Enlace al texto completo (gratis o de pago) [1038/aps.2013.98](#)

**AUTORES / AUTHORS:** - Wang SG; Huang MH; Li JH; Lai FI; Lee HM; Hsu YN

**INSTITUCIÓN / INSTITUTION:** - 1] Institute of Pharmaceutical Science and Technology, Central Taiwan University of Science and Technology, Taichung, Taiwan, China [2] Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung, Taiwan, China.

**RESUMEN / SUMMARY:** - Aim: To investigate the effects of punicalagin, a polyphenol isolated from Punica granatum, on human U87MG glioma cells in vitro. Methods: The viability of human U87MG glioma cells was evaluated using MTT assay. Cell cycle was detected with flow cytometry analysis. The levels of Bcl-2, cleaved caspase-9, cleaved poly(ADP-ribose) polymerase (PARP), phosphor-AMPK and phosphor-p27 at Thr198

were measured using immunoblot analyses. Caspase-3 activity was determined with spectrophotometer. To determine autophagy, LC3 cleavage and punctate patterns were examined. Results: Punicalagin (1-30 µg/mL) dose-dependently inhibited the cell viability in association with increased cyclin E level and decreased cyclin B and cyclin A levels. The treatment also induced apoptosis as shown by the cleavage of PARP, activation of caspase-9, and increase of caspase-3 activity in the cells. However, pretreatment of the cells with the pan-caspase inhibitor z-DEVD-fmk (50 µmol/L) did not completely prevent the cell death. On the other hand, punicalagin treatment increased LC3-II cleavage and caused GFP-LC3-II-stained punctate pattern in the cells. Suppressing autophagy of cells with chloroquine (1-10 µmol/L) dose-dependently alleviated the cell death caused by punicalagin. Punicalagin (1-30 µg/mL) also increased the levels phosphor-AMPK and phosphor-p27 at Thr198 in the cells, which were correlated with the induction of autophagic cell death. Conclusion: Punicalagin induces human U87MG glioma cell death through both apoptotic and autophagic pathways.

[768]

**TÍTULO / TITLE:** - Markers for Anti-cytotoxic T-lymphocyte Antigen 4 (CTLA-4) Therapy in Melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1102:83-95. doi: 10.1007/978-1-62703-727-3\_6.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-727-3\\_6](#)

**AUTORES / AUTHORS:** - Postow MA; Yuan J; Kitano S; Lesokhin AM; Wolchok JD

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

**RESUMEN / SUMMARY:** - Therapeutic strategies that block Cytotoxic T lymphocyte antigen-4 (CTLA-4) enhance antitumor immunity and prolong the lives of patients with metastatic melanoma. However, only a subset of patients benefit, and responses are often delayed due to heterogeneous response kinetics. Ongoing monitoring of the immunologic effects of therapy and correlating these immunologic changes with patient outcomes continue to be important goals to better identify possible mechanisms of clinical activity of these agents. This chapter introduces the major areas of investigation in monitoring patients treated with CTLA-4 blockade and provides specific details of our experience performing selected assays.

[769]

**TÍTULO / TITLE:** - Prognostic relevance at 5 years of the early monitoring of neoadjuvant chemotherapy using F-FDG PET in luminal HER2-negative breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Nucl Med Mol Imaging. 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1007/s00259-013-2616-3](#)

**AUTORES / AUTHORS:** - Humbert O; Berrilo-Riedinger A; Cochet A; Gauthier M; Charon-Barra C; Guiu S; Desmoulins I; Toubreau M; Dygai-Cochet I; Coutant C; Fumoleau P; Brunotte F

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, Centre GF Leclerc, 1 rue du Pr Marion, 21000, Dijon, France, [ohumbert@cgfl.fr](mailto:ohumbert@cgfl.fr).

**RESUMEN / SUMMARY:** - PURPOSE: The objective of this study was to evaluate, in the luminal human epidermal growth factor receptor 2 (HER2)-negative breast cancer subtype, the prognostic value of tumour glucose metabolism at baseline and of its early changes during neoadjuvant chemotherapy (NAC). METHODS: This prospective study included 61 women with hormone-sensitive HER2-negative breast cancer treated with NAC. 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) was performed at baseline. Hepatic activity was used as a reference to distinguish between low metabolic and hypermetabolic tumours. In hypermetabolic tumours, a PET exam was repeated after the first course of NAC. The relative change in the maximum standardized uptake value of the tumour (SUV) was calculated. RESULTS: Nineteen women had low metabolic luminal breast cancers at baseline, correlated with low proliferation indexes. Forty-two women had hypermetabolic tumours, corresponding to more proliferative breast cancers with higher Ki-67 expression ( $p = 0.017$ ) and higher grade ( $p = 0.04$ ). The median follow-up period was 64.2 months (range 11.5-93.2). Thirteen women developed recurrent disease, nine of whom died. Worse overall survival was associated with larger tumour size [ $>5$  cm, hazard ratio (HR) = 6.52,  $p = 0.009$ ] and with hypermetabolic tumours achieving a low metabolic response after one cycle of NAC (DeltaSUV  $< 16$  %, HR = 10.63,  $p = 0.004$ ). Five-year overall survival in these poor responder patients was 49.2 %. Overall survival in women with low metabolic tumours or hypermetabolic/good response tumours was 100 and 96.15 %, respectively. CONCLUSION: In luminal HER2-negative breast tumours, tumour metabolism at baseline and changes after the first course of NAC are early surrogate markers of patients' survival. A subgroup of women with hypermetabolic/poorly responding tumours, correlated with poor prognosis at 5 years, can be identified early. These results may guide future studies by tailoring the NAC regimen to the metabolic response.

[770]

**TÍTULO / TITLE:** - Curcumin attenuates amyloid-beta-induced tau hyperphosphorylation in human neuroblastoma SH-SY5Y cells involving PTEN/Akt/GSK-3beta signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Recept Signal Transduct Res. 2013 Nov 4.

●● Enlace al texto completo (gratis o de pago) [3109/10799893.2013.848891](#)

**AUTORES / AUTHORS:** - Huang HC; Tang D; Xu K; Jiang ZF

**INSTITUCIÓN / INSTITUTION:** - Beijing Key Laboratory of Bioactive Substances and Functional Foods, Beijing Union University, Beijing, People's Republic of China.

**RESUMEN / SUMMARY:** - Abstract Accumulated amyloid-beta peptide (A $\beta$ ) and hyperphosphorylated tau proteins are two hallmarks of Alzheimer's disease (AD). Increasing evidence suggests that A $\beta$  induces tau hyperphosphorylation in AD pathology, but the signaling pathway is not completely understood. Inhibiting A $\beta$ -induced cellular signaling is beneficial to AD treatment. In this study, cellular signaling of tau phosphorylation induced by A $\beta$  and the inhibiting effects of curcumin on this signaling were investigated on human neuroblastoma SH-SY5Y cells. The results indicated that curcumin inhibits A $\beta$ -induced tau phosphorylation at Thr231 and

Ser396, over-expression of HDAC6, and decrease in phosphorylation of glycogen synthase kinase-3beta (GSK-3beta) at Ser9. However, the protective effect of curcumin on dephosphorylation of GSK-3beta induced by Abeta is not directly related to cellular oxidative stress. Curcumin depresses Abeta-induced down-regulation of phosphorylations of Akt at Thr308 and Ser473 and 3-phosphoinositide-dependent protein kinase 1 at Ser241, implying that second message PIP3 involves curcumin-protective cell signaling. Furthermore, insulin receptor/phosphatidylinositol 3-kinase pathway, as a regulatory signaling of second message PIP3, does not participate in Abeta-induced deactivation of Akt (dephosphorylation at Thr308 and Ser473). However, Abeta results in over-expression of Phosphatase and tensin homolog (PTEN), a negative regulator of PIP3. Curcumin depresses Abeta-induced up-regulation of PTEN induced by Abeta. These results imply that curcumin inhibits Abeta-induced tau hyperphosphorylation involving PTEN/Akt/GSK-3beta pathway.

[771]

**TÍTULO / TITLE:** - AXL/epidermal growth factor receptor (EGFR) complexes in breast cancer - culprits for resistance to EGFR inhibitors?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast Cancer Res. 2013 Oct 29;15(5):315.

●● Enlace al texto completo (gratis o de pago) [1186/bcr3564](#)

**AUTORES / AUTHORS:** - Heideman MR; Hynes NE

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**RESUMEN / SUMMARY:** - Epidermal growth factor receptor (EGFR) is highly expressed in triple-negative breast cancer (TNBC), and elevated levels correlate with poor prognosis. In analogy with the paradigm of oncogene addiction, blocking EGFR in TNBC was expected to have clinical efficacy - but this has not been the case. Reasons for these results have remained elusive. Recently, Meyer and colleagues showed interplay between EGFR and the epithelial-to-mesenchymal transition-associated AXL receptor in TNBC cells, which might provide some clues.

[772]

**TÍTULO / TITLE:** - The tumor suppressing effects of QKI-5 in prostate cancer: A novel diagnostic and prognostic protein.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Oct 23;15(1).

**AUTORES / AUTHORS:** - Zhao Y; Zhang G; Wei M; Lu X; Fu H; Feng F; Wang S; Lu W; Wu N; Lu Z; Yuan J

**INSTITUCIÓN / INSTITUTION:** - Department of Urology; Xijing Hospital; Fourth Military Medical University; Xi'an, PR China; Department of Biochemistry and Molecular Biology; State Key Laboratory of Cancer Biology; Fourth Military Medical University; Xi'an, PR China.

**RESUMEN / SUMMARY:** - In recent years, the RNA-binding protein quaking 5 (QKI-5) has been recognized as a novel tumor suppressor in many cancers. To date, no studies have examined the role of QKI-5 in prostate cancer. The present study was

designed to elucidate the correlation of QKI-5 expression with the clinical pathological features and prognosis of prostate cancer. In an overwhelming majority of the 184 cases of prostate cancer samples analyzed, the QKI-5 expression was significantly decreased, which was largely due to the high promoter methylation levels. Using lentiviral vectors, we established two stable prostate cancer cell lines with altered QKI-5 expression, including a QKI-5 overexpressing PC3 cell line and a DU145 cell line with knocked-down QKI-5 expression. The effects of the lentiviral-mediated QKI-5 knockdown on the PC3 cells and DU145 cells were assessed by cell growth curves, flow cytometry (FCM), and an invasion assay. The PC3 cells were transplanted into nude mice, and then, the tumor growth curves and TUNEL staining were determined. These results demonstrated that QKI-5 was highly expressed in benign prostatic hyperplasia (BPH) tissues but not in carcinomatous tissues and that QKI-5 effectively inhibited prostate cancer cell proliferation in vitro and in vivo. In addition, the decrease in QKI-5 expression was closely correlated with the prostate cancer Gleason score, poor differentiation, degree of invasion, lymph node metastasis, distant metastasis, TNM grading, and poor survival. These results indicate that the QKI-5 expression may be a novel, independent factor in the prognosis of prostate cancer patients.

[773]

**TÍTULO / TITLE:** - Level of TNF-related apoptosis-inducing-ligand and CXCL8 correlated with 2-[18F]Fluoro-2-deoxy-D-glucose uptake in anti-VEGF treated colon cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Med Sci Monit. 2013 Oct 21;19:875-82. doi: 10.12659/MSM.889605.

●● Enlace al texto completo (gratis o de pago) [12659/MSM.889605](#)

**AUTORES / AUTHORS:** - Celik B; Yalcin AD; Bisgin A; Dimitrakopoulou-Strauss A; Kargi A; Strauss LG

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Antalya Education and Research Hospital, Antalya, Turkey.

**RESUMEN / SUMMARY:** - Background The changes and correlations of TRAIL (TNF-related apoptosis-inducing-ligand) and CXCL8 (IL8) prior to treatment and three months following therapy as well as the corresponding Positron emission tomography (PET/CT) (SUVmax: standardized uptake maximum values) results were evaluated. Material and Methods The measurements were taken before and after treatment for comparison purposes. The study population comprised 29 patients with Metastatic Colorectal cancer (MCR), undergoing PET/CT scanning prior to treatment. Results There were significant changes prior to treatment and three months later for sTRAIL ( $p=0.0080$ ) and CXCL8 ( $p=0.0001$ ) values. Generally, sTRAIL values were increasing during therapy, while a decrease was observed for CXCL8. Correlation analysis was applied to the data and revealed significant correlations for the SUVmax in the primary tumor prior to treatment and CXCL8 prior to therapy ( $p=0.0303$ ). Furthermore, significant correlations were observed for the SUVmax and sTRAIL ( $p=0.0237$ ) as well as CXCL8 ( $p=0.0002$ ) three months after treatment initiation. CXCL8 prior to treatment was also correlated with the SUV three months after onset of treatment ( $p=0.0072$ ). A significant correlation was noted for one combination of two variables, the SUVmax in the metastases and CXCL8 prior to treatment ( $p=0.0175$ ). These results are supported

when we group the SUVmax in the metastases following treatment into two groups with SUVmax <5 and SUVmax >5. Conclusions This study provides evidence that proteomics patterns of sTRAIL and CXCL8 predict tumor response and survival in MCRC patients treated with bevacizumab and within a high concordance of FDG-PET/CT findings.

[774]

**TÍTULO / TITLE:** - Curcumin decreases oleic acid-induced lipid accumulation via AMPK phosphorylation in hepatocarcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur Rev Med Pharmacol Sci. 2013 Oct;17(19):2578-86.

**AUTORES / AUTHORS:** - Kang OH; Kim SB; Seo YS; Joung DK; Mun SH; Choi JG; Lee YM; Kang DG; Lee HS; Kwon DY

**INSTITUCIÓN / INSTITUTION:** - Department of Oriental Pharmacy, College of Pharmacy, Wonkwang University, Wonkwang Oriental Medicines Research Institute, Institute of Biotechnology, Iksan, Jeonbuk, Republic of Korea. [sssimi@wonkwang.ac.kr](mailto:sssimi@wonkwang.ac.kr)

**RESUMEN / SUMMARY:** - BACKGROUND AND OBJECTIVES: Non-alcoholic fatty liver disease (NAFLD) is one of the most common metabolic syndromes and is characterized by the accumulation of hepatic triglycerides (TG), which result from an imbalance between uptake, synthesis, export, and oxidation of fatty acids. Curcumin is a polyphenol derived from the herbal remedy and dietary spice turmeric, was found to prevent obesity and diabetes in mouse models. However, a hypolipidemic effect of curcumin in oleic acid-induced hepatocarcinoma cells has not been reported. In this study, we examined the effect of curcumin on reducing lipid accumulation in hepatic cells. MATERIALS AND METHODS: Hepatocytes were treated with oleic acid (OA) containing with or without curcumin to observe the lipid accumulation by Oil Red O stain. We also tested the effects of curcumin on triglycerides (TG) and total cholesterol (TC) in HepG2 cells. Western blot and reverse transcription polymerase chain reaction (RT-PCR) was used to measure sterol regulatory element binding proteins-1 (SREBP-1), fatty acid synthase (FAS), peroxisome proliferator-activated receptor (PPAR)-alpha, and adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) expression. RESULTS: Curcumin suppressed OA-induced lipid accumulation and TG and TC levels. Also, curcumin decreased hepatic lipogenesis such as SREBP-1, and FAS. Besides, we also found out the antioxidative effect of curcumin by increasing the expression of PPARalpha. Curcumin increased AMPK phosphorylation in hepatocytes. CONCLUSIONS: These results indicated that curcumin has the same ability to activate AMPK and then reduce SREBP-1, and FAS expression, finally leading to inhibit hepatic lipogenesis and hepatic antioxidative ability. In this report, we found curcumin exerted a regulatory effect on lipid accumulation by decreasing lipogenesis in hepatocyte. Therefore, curcumin extract may be active in the prevention of fatty liver.

[775]

**TÍTULO / TITLE:** - Can Behenic Acid (C22:0) Levels be a Prognostic Factor in Glial Tumors?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Can J Neurol Sci. 2013 Nov;40(6):854-6.

**AUTORES / AUTHORS:** - Kaplan M; Koparan M; Sari A; Ozturk S; Kaplan SK; Erol FS

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[776]

**TÍTULO / TITLE:** - Role of cyclin polymorphisms in predicting outcome of 5-fluorouracil-based chemotherapy in colorectal cancer: one piece in a complex puzzle.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Nov;14(14):1671-4. doi: 10.2217/pgs.13.138.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.138](#)

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[777]

**TÍTULO / TITLE:** - HOTAIR, a cell cycle-associated long noncoding RNA and a strong predictor of survival, is preferentially expressed in classical and mesenchymal glioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neuro Oncol. 2013 Dec;15(12):1595-603. doi: 10.1093/neuonc/not131. Epub 2013 Nov 7.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not131](#)

**AUTORES / AUTHORS:** - Zhang JX; Han L; Bao ZS; Wang YY; Chen LY; Yan W; Yu SZ; Pu PY; Liu N; You YP; Jiang T; Kang CS

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**RESUMEN / SUMMARY:** - Background Long noncoding RNA Hox transcript antisense intergenic RNA (HOTAIR) has been characterized as a negative prognostic factor in breast and colon cancer patients. The clinical significance and function of HOTAIR in glioma remains unclear. Methods We analyzed the clinical significance of HOTAIR in 3 different glioma cohorts with gene expression data, including correlation with tumor grade, prognosis, and molecular subtype. The function of HOTAIR in glioma was explored by performing gene set enrichment analysis and in vitro and in vivo experiments. Results HOTAIR expression was closely associated with glioma grade and poor prognosis. Multivariate Cox regression analysis revealed that HOTAIR was an independent prognostic factor in glioblastoma multiforme patients. HOTAIR expression correlated with glioma molecular subtype, including those of The Cancer Genome Atlas. HOTAIR was preferentially expressed in the classical and mesenchymal subtypes compared with the neural and proneural subtypes. A gene set enrichment analysis designed to show gene set differences between patients with high and low HOTAIR expression indicated that HOTAIR expression was associated with gene sets involved in cell cycle progression. HOTAIR reduction induced colony formation suppression, cell cycle G0/G1 arrest, and orthotopic tumor growth inhibition.

Conclusion Our data establish that HOTAIR is an important long noncoding RNA that primarily serves as a prognostic factor for glioma patient survival, as well as a biomarker for identifying glioma molecular subtypes, a critical regulator of cell cycle progression.

[778]

**TÍTULO / TITLE:** - Prognostic molecular markers in head and neck squamous cell carcinoma in a New Zealand population: matrix metalloproteinase-2 and sialyl Lewis x antigen.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - ANZ J Surg. 2013 Oct 31. doi: 10.1111/ans.12424.

●● Enlace al texto completo (gratis o de pago) [1111/ans.12424](#)

**AUTORES / AUTHORS:** - Gunawardena I; Arendse M; Jameson MB; Plank LD; Gregor RT

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology-Head and Neck Surgery, Waikato Hospital, Hamilton, New Zealand.

**RESUMEN / SUMMARY:** - OBJECTIVE: The survival rate for head and neck squamous cell carcinoma (HNSCC) is among the lowest of the major cancers and has not substantially improved in the past two decades. Tumours with similar histological features may have widely differing clinical outcomes and thus identification of prognostic and predictive biomarkers may be valuable for determining appropriate clinical management strategies. The objective of this study was to establish the prognostic significance of six molecular markers in HNSCC in a New Zealand population: matrix metalloproteinases 2 and 9 (MMP-2, MMP-9), tissue inhibitor of matrix metalloproteinase-1, sialyl Lewis antigens a and x (sLea, sLex) and alpha B-crystallin. METHODS: Retrospective review of 145 sequential HNSCC patients from a tertiary centre with minimum 3 years surveillance. Sections from formalin-fixed paraffin-embedded tumour blocks were immunostained for the molecular markers and scored. Cox regression modelling was used to adjust for potential confounding variables impacting on cancer survival. RESULTS: Multivariate analysis for individual biomarkers, controlling for age, sex, tumour grade, N-stage, T-stage, tumour site, smoking history and alcohol use, revealed poorer survival with tumour expression of MMP-2 (hazard ratio = 1.98, 95% confidence interval: 1.11-3.52, P = 0.021) and sLex (hazard ratio = 3.22, 95% confidence interval: 1.33-7.80, P = 0.010). A stepwise analysis showed that MMP-2 and sLex were independently prognostic after covariate adjustment. CONCLUSIONS: MMP-2 and sLex were negative prognostic markers for survival in these HNSCC patients. This offers opportunities for clinical trials to reduce the risk of nodal and distant metastases through blocking tumour cell adhesion to endothelium.

[779]

**TÍTULO / TITLE:** - Design and Evaluation of Folate-Appended alpha-, beta-, and gamma-Cyclodextrins Having a Caproic Acid as a Tumor Selective Antitumor Drug Carrier in Vitro and in Vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomacromolecules. 2013 Nov 21.

- Enlace al texto completo (gratis o de pago) [1021/bm401340g](https://doi.org/10.2174/157231413401340g)

**AUTORES / AUTHORS:** - Okamatsu A; Motoyama K; Onodera R; Higashi T; Koshigoe T; Shimada Y; Hattori K; Takeuchi T; Arima H

**INSTITUCIÓN / INSTITUTION:** - Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973, Japan.

**RESUMEN / SUMMARY:** - We reported that per-6-folic acid (FA)-appended beta-cyclodextrin (beta-CyD) possessing two caproic acids between FA and a beta-CyD molecule as a spacer (Fol-c2-beta-CyD) could be useful as a promising antitumor drug carrier. However, the effects of the cavity size and the spacer length on the carrier ability are not still known. In this study, we designed and evaluated the FA-appended three kinds of CyDs possessing a caproic acid as a spacer between FA and a CyD molecule (Fol-c1-CyDs) as a tumor targeting carrier for antitumor drugs. The stability constant of the Fol-c1-beta-CyD/doxorubicin (DOX) complex was much higher than those of Fol-c1-alpha-CyD and Fol-c1-gamma-CyD at pH 7.3. Antitumor activity of DOX was increased by the complexation with Fol-c1-beta-CyD, but not with Fol-c1-alpha-CyD or Fol-c1-gamma-CyD in KB cells, a folate receptor-alpha-positive cell line. Also, Fol-c1-beta-CyD increased antitumor activities of paclitaxel and vinblastine, but not 5-fluorouracil. Furthermore, Fol-c1-beta-CyD accelerated cellular uptake of DOX and inhibited its efflux from KB cells. The Fol-c1-beta-CyD/DOX complex showed much higher antitumor activity than DOX alone after intratumoral and intravenous administrations to tumor-bearing mice with a negligible change of the blood chemistry values. These findings suggest that Fol-c1-beta-CyD could be useful as a tumor-selective carrier for antitumor drugs.

[780]

**TÍTULO / TITLE:** - Who Benefits Most From Adjuvant Interferon Treatment for Melanoma?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Ther. 2013 Oct 30.

- Enlace al texto completo (gratis o de pago)

[1097/MJT.0b013e31829e883d](https://doi.org/10.1097/MJT.0b013e31829e883d)

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**RESUMEN / SUMMARY:** - Metastatic melanoma has a poor prognosis; the median survival for patients with stage IV melanoma ranges from 8 to 18 months after diagnosis. Interferon-alpha provides significant improvement in disease-free survival at the cost of poor tolerability. Identifying patients who benefit the most may improve the

cost:benefit ratio. In addition, no data exist for the role of adjuvant therapy in noncutaneous melanoma. Molecular profiles may help to identify patients who benefit the most from adjuvant interferon therapy. In this review, the American Joint Commission on Cancer 2009 staging criteria and emerging biomarker data to guide adjuvant treatment decisions will be discussed. Several criteria to guide selection of patients are discussed in detail. These include Breslow thickness, number of positive lymph nodes, whether or not the primary lesion has ulcerated, immunologic markers, and cytokine profiles. Substantial progress has been made in deciding which patients benefit from interferon-alpha adjuvant therapy. Interferon-alpha is the only agent currently approved for the adjuvant treatment of this deadly disease, despite its side effect profile. More effective drugs with better tolerability are needed.

[781]

**TÍTULO / TITLE:** - Discovery of a potent dual EGFR/HER-2 inhibitor L-2 (selatinib) for the treatment of cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 Nov;69:833-41. doi: 10.1016/j.ejmech.2013.09.032. Epub 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.09.032](#)

**AUTORES / AUTHORS:** - Zhang L; Fan C; Guo Z; Li Y; Zhao S; Yang S; Yang Y; Zhu J; Lin D

**INSTITUCIÓN / INSTITUTION:** - Qilu Institute of Pharmaceutical Research, Qilu Pharmaceutical Co. Ltd, 243 Gong Ye Bei Road, Jinan 250100, Shandong Province, PR China.

**RESUMEN / SUMMARY:** - To develop potent dual EGFR/HER-2 inhibitors with improved druggability, a series of new lapatinib analogs were designed and synthesized. Compared with lapatinib, L-2, L-4 and M-6 were more active against BT-474 or NCI-N87 cells. In vivo efficacy studies indicated that L-2 significantly suppressed tumor growth in NCI-N87 (94.8% inhibition) or SK-OV-3 xenograft (85.7% inhibition) without causing significant loss of body weight. And the inhibition rates of lapatinib in the two xenograft models were 89.7% and 78.8%, respectively. Moreover, further studies revealed that the potent in vivo activities of L-2 may be mainly attributed to its superior aqueous solubility and oral bioavailability. In addition, a high-yielding one-pot procedure was developed for the synthesis of lapatinib and its analogs.

[782]

**TÍTULO / TITLE:** - Angiogenesis inhibitors in the treatment of prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chem Immunol Allergy. 2014;99:197-215. doi: 10.1159/000353255. Epub 2013 Oct 17.

●● Enlace al texto completo (gratis o de pago) [1159/000353255](#)

**AUTORES / AUTHORS:** - Adesunloye BA; Karzai FH; Dahut WL

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Branch, National Cancer Institute, Bethesda, Md., USA.

**RESUMEN / SUMMARY:** - Prostate cancer is the most common cancer in men in the United States and is the second most common cause of death. While treatment

options in early stage disease are curative in intent, treatment of metastatic prostate cancer remains challenging. Although, several new and promising treatment options exploiting novel targets have permeated the therapeutic landscape in recent years, another viable target for therapy is tumor angiogenesis. Many antiangiogenic agents are under development and some are currently under investigation in clinical trials.

[783]

**TÍTULO / TITLE:** - Combination of hemoglobin, alkaline phosphatase, and age predicts optimal docetaxel regimen for patients with castration-resistant prostate cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Oncol. 2013 Nov 23.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10147-013-0638-2](#)

**AUTORES / AUTHORS:** - Matsuyama H; Shimabukuro T; Hara I; Kohjimoto Y; Suzuki K; Koike H; Uemura H; Hayashi T; Ueno M; Kodaira K; Tomita Y; Sakurai T; Shimizu N

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-kogushi, Ube, Yamaguchi, 755-8505, Japan, [hidde@yamaguchi-u.ac.jp](mailto:hidde@yamaguchi-u.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: We aimed to find the prognostic factors predicting overall survival (OS) in patients with castration-resistant prostate cancer (CRPC) who had docetaxel (DTX) chemotherapy, and to construct a model predicting the optimum number of cycles of DTX. METHODS: A total of 279 CRPC patients who received DTX ( $\geq 50$  mg/m<sup>2</sup>) every 3-4 weeks were studied retrospectively. Prognostic factors predicting treatment cycles as well as OS were analyzed, and a risk table for predicting treatment cycles was constructed. RESULTS: The longer treatment group ( $>10$  cycles) had a significantly longer OS than the standard treatment group ( $p < 0.0001$ ). Multivariate analysis demonstrated that a decrease of  $\geq 50$  % in prostate-specific antigen (PSA), serum markers at the start of DTX therapy [PSA, alkaline phosphatase (ALP), and C-reactive protein (CRP)], and the number of DTX courses were independent predictors of OS. The risk table employing the combination of three factors [ALP (cut-off 189 IU/L), hemoglobin (11.3 g/dL), and age (65 years) at the start of DTX therapy], and scoring based on the hazard ratio of each risk factor (ALP 4, hemoglobin 2, age 3) could effectively predict the probability of the length of DTX therapy, with lower score (0-6) predicting  $>10$  cycles, and higher score (7-9) predicting  $\leq 5$  cycles ( $p < 0.0001$ ). No significant difference was found regarding grade  $\geq 3$  adverse events between the two groups. CONCLUSION: A model using three factors prior to chemotherapy may be beneficial for deciding the duration of DTX therapy in patients with CRPC.

[784]

**TÍTULO / TITLE:** - MicroRNAs: key players of taxane resistance and their therapeutic potential in human cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Mol Med. 2013 Oct;17(10):1207-17. doi: 10.1111/jcmm.12131. Epub 2013 Sep 23.

●● [Enlace al texto completo \(gratis o de pago\) 1111/jcmm.12131](#)

**AUTORES / AUTHORS:** - Cui SY; Wang R; Chen LB

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, School of Medicine, Jinling Hospital, Nanjing University, Nanjing, Jiangsu, China.

**RESUMEN / SUMMARY:** - The successful long-term use of taxane for cancer therapy is often prevented by the development of drug resistance in clinic. Thus, exploring the mechanisms involved is a first step towards rational strategies to overcome taxane resistance. Taxane resistance-related microRNA (miRNAs) are under investigation and miRNAs could induce the taxane resistance of tumour cells by regulating cell cycle distribution, survival and/or apoptosis pathways, drug transports, epithelial-mesenchymal transition and cancer stem cell. This article summarizes current research involving miRNAs as regulators of key target genes for taxane chemoresistance and discusses the complex regulatory networks of miRNAs. Also, the authors will envisage future developments towards the potential use of targeting miRNAs as a novel strategy for improving response of tumour patients to taxane. miRNAs play critical roles in taxane chemoresistance and the miRNA-based therapies will be helpful for overcoming drug resistance and developing more effective personalized anti-cancer treatment strategies. Further research studies should be performed to promote therapeutic-clinical use of taxane resistance-related miRNAs in cancer patients, especially in those patients with taxane-resistant cancers.

[785]

**TÍTULO / TITLE:** - Study of the therapeutic effect of 188Re labeled folate targeting albumin nanoparticle coupled with cis-Diamminedichloroplatinum Cisplatin on human ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Mater Eng. 2014;24(1):711-22. doi: 10.3233/BME-130859.

●● Enlace al texto completo (gratis o de pago) [3233/BME-130859](#)

**AUTORES / AUTHORS:** - Tang Q; Chen D

**INSTITUCIÓN / INSTITUTION:** - School of Medical Science, Southeast University, No. 87, Dingjiaqiao Road, Nanjing 210009, Jiangsu Province, China.

**RESUMEN / SUMMARY:** - This paper aimed to investigate the treatment efficiency of 188Re labeled folate targeting albumin nanoparticles with cis-Diamminedichloroplatinum Cisplatin (188Re-folate-CDDP/HAS MNP) on human ovarian cancer. SKOV3 cells or tumor-bearing mice were divided into different groups and treated as follow: (A) negative control; (B) chemotherapy; (C) radiotherapy; (D) hyperthermia; (E) chemotherapy and radiotherapy; (F) chemotherapy and hyperthermia; (G) radiotherapy and hyperthermia; (H) chemotherapy, radiotherapy and hyperthermia. Treatment of B to H inhibited proliferation of SKOV3 cells, with the greatest inhibition being observed in group H ( $P < 0.05$ ). Obvious apoptotic hypodiploid peak appeared beside G1 phase in groups of B to H. The apoptotic rates of SKOV3 cells in groups of A to H were 0.08%, 7.56%, 8.64%, 17.14%, 21.64%, 23.77%, 33.94% and 57.16%, respectively. Our findings in vivo study showed that the mass of tumor in each group of B to H was significantly lower than that in the negative control ( $p < 0.05$ ). In addition, compared with each group of B to G, group H showed highest inhibition of tumor growth ( $p < 0.05$ ). In conclusion, the combination of magnetic induced hyperthermia, chemotherapy and targeted radionuclide of radiation exposure can

effectively inhibit the growth of ovarian cancer, which indicates a potential applications in ovarian cancer treatment.

[786]

**TÍTULO / TITLE:** - Combination therapy targeting integrins reduces glioblastoma tumor growth through antiangiogenic and direct antitumor activity and leads to activation of the pro-proliferative prolactin pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer. 2013 Nov 20;12(1):144.

- Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-144](#)

**AUTORES / AUTHORS:** - Oliveira-Ferrer L; Wellbrock J; Bartsch U; Murga Penas EM; Hauschild J; Klokow M; Bokemeyer C; Fiedler W; Schuch G

**RESUMEN / SUMMARY:** - BACKGROUND: Tumors may develop resistance to specific angiogenic inhibitors via activation of alternative pathways. Therefore, multiple angiogenic pathways should be targeted to achieve significant angiogenic blockade. In this study we investigated the effects of a combined application of the angiogenic inhibitors endostatin and tumstatin in a model of human glioblastoma multiforme. RESULTS: Inhibitors released by stably transfected porcine aortic endothelial cells (PAE) showed anti-angiogenic activity in proliferation and wound-healing assays with endothelial cells (EC). Interestingly, combination of endostatin and tumstatin (ES + Tum) also reduced proliferation of glioma cells and additionally induced morphological changes and apoptosis in vitro. Microencapsulated PAE-cells producing these inhibitors were applied for local therapy in a subcutaneous glioblastoma model. When endostatin or tumstatin were applied separately, in vivo tumor growth was inhibited by 58% and 50%, respectively. Combined application of ES + Tum, in comparison, resulted in a significantly more pronounced inhibition of tumor growth (83%). cDNA microarrays of tumors treated with ES + Tum revealed an up-regulation of prolactin receptor (PRLR). ES + Tum-induced up-regulation of PRLR in glioma cells was also found in vitro. Moreover, exogenous PRLR overexpression in vitro led to up-regulation of its ligand prolactin and increased proliferation suggesting a functional autocrine growth loop in these cells. CONCLUSION: Our data indicate that integrin-targeting factors endostatin and tumstatin act additively by inhibiting glioblastoma growth via reduction of vessel density but also directly by affecting proliferation and viability of tumor cells. Treatment with the ES + Tum-combination activates the PRLR pro-proliferative pathway in glioblastoma. Future work will show whether the prolactin signaling pathway represents an additional target to improve therapeutic strategies in this entity.

[787]

**TÍTULO / TITLE:** - Platin polymorphisms predict gender and stage-specific colon cancer recurrence after adjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Oct 29.

- Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-](#)

[0646](#)

**AUTORES / AUTHORS:** - Ning Y; Gerger A; Zhang W; Hanna DL; Yang D; Winder T; Wakatsuki T; Labonte MJ; Stintzing S; Volz N; Sunakawa Y; Stremitzer S; El-Khoueiry R; Lenz HJ

**INSTITUCIÓN / INSTITUTION:** - 1Division of Medical Oncology, University of Southern California, Norris Comprehensive Cancer Center.

**RESUMEN / SUMMARY:** - Tumor recurrence after curative resection remains a major problem in patients with locally advanced colorectal cancer (CRC) treated with adjuvant chemotherapy. Genetic single nucleotide polymorphisms (SNPs) may serve as useful molecular markers to predict clinical outcomes in these patients and identify targets for future drug development. Recent in vitro and in vivo studies have demonstrated that the platin genes, PLS3 and LCP1, are overexpressed in colon cancer cells and play an important role in tumor cell invasion, adhesion and migration. Hence, we hypothesized that functional genetic variations of platin may direct effects on the progression and prognosis of locally advanced CRC. We tested whether functional tagging polymorphisms of PLS3 and LCP1 predict time to tumor recurrence (TTR) in 732 patients (training set: 234; validation set: 498) with stage II/III CRC. The PLS3 rs11342 and LCP1 rs4941543 polymorphisms were associated with a significantly increased risk for recurrence in the training set. PLS3 rs6643869 showed a consistent association with TTR in the training and validation set, when stratified by gender and tumor location. Female patients with the PLS3 rs6643869 AA genotype had the shortest median TTR compared to those with any G allele in the training set [1.7 vs. 9.4 years; HR 2.84(95% CI=1.32-6.1); p=0.005] and validation set [3.3 vs. 13.7 years; HR 2.07 (95%CI=1.09-3.91); p=0.021]. Our findings suggest that several SNPs of the PLS3 and LCP1 genes could serve as gender and/or stage-specific molecular predictors of tumor recurrence in stage II/III CRC patients as well as potential therapeutic targets.

[788]

**TÍTULO / TITLE:** - Prognostic significance of epidermal growth factor receptor overexpression in pancreas cancer and nodal metastasis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - ANZ J Surg. 2013 Sep 25. doi: 10.1111/ans.12399.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ans.12399](#)

**AUTORES / AUTHORS:** - Perini MV; Montagnini AL; Coudry R; Patzina R; Penteadó S; Abdo EE; Diniz A; Jukemura J; da Cunha JE

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Surgical Division, University of Sao Paulo Medical School, Sao Paulo, Brazil.

**RESUMEN / SUMMARY:** - BACKGROUND: Identification of molecular markers in pancreatic adenocarcinoma (PA) has the potential to guide targeted therapy. The objective of this study is to determine the prognostic significance of epidermal growth factor receptor (EGFR) expression (membrane and cytoplasmic) in resected PA and its correlation with lymph node metastasis and survival. METHODS: EGFR overexpression was determined by immunohistochemistry, and the pattern of expression was compared between the primary tumour, adjacent normal pancreas and involved lymph nodes. RESULTS: A total of 88 patients had curative resection. No difference was found in mEGFR overexpression between tumoural and metastatic nodal tissues (P = 0.28). Median overall survival time was 22.9 months. Overall

cumulative 1-, 3- and 5-year survival was 48%, 20% and 18%, respectively. In positive mEGFR tumour expression, survival was 46% at 1 year, 8% at 3 years and 0% at 5 years ( $P < 0.05$ ). Univariate analysis showed that male gender, portal vein (PV) resection, perineural, lymphovascular and peri-pancreatic invasion, positive margins and positive mEGFR expression in tumour tissue had worse survival. Multivariate analysis showed that male gender, PV resection, vascular and perineural invasion remained independent predictors of poor survival. CONCLUSION: Positive mEGFR overexpression is associated with decreased survival; however, it is not an independent prognostic factor.

[789]

**TÍTULO / TITLE:** - Feasibility study of docetaxel and cyclophosphamide six- cycle therapy as adjuvant chemotherapy for Japanese human epidermal growth factor receptor 2-negative breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(8):4835-8.

**AUTORES / AUTHORS:** - Abe H; Mori T; Kawai Y; Tomida K; Kubota Y; Umeda T; Tani T

**INSTITUCIÓN / INSTITUTION:** - Breast Center, Belle Land General Hospital, Osaka, Japan E-mail : [abe@belle.shiga-med.ac.jp](mailto:abe@belle.shiga-med.ac.jp).

**RESUMEN / SUMMARY:** - BACKGROUND: We compared treatment completion rates and safety of docetaxel and cyclophosphamide six- cycle therapy (TC6) with docetaxel followed by 5FU, epirubicin and cyclophosphamide (T-FEC) therapy in Japanese patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer. MATERIALS AND METHODS: We administered TC6 q3w or T-FEC q3w to HER2-negative breast cancer patients. The primary endpoint of this trial was toxicity. As second endpoints, the treatment completion rate and relative dose intensity were evaluated. RESULTS: The TC6 and T-FEC group consisted of 22 and 21 patients, respectively. Concerning hematological toxicity, grade 3 or higher adverse reactions included neutropenia and febrile neutropenia. As non-hematological adverse events, exanthema and peripheral neuropathy were frequently reported in the TC6 group, whereas more patients of the T-FEC group reported nausea and vomiting. In TC6, the treatment completion rate was 86.4% and the relative dose intensity of docetaxel was 93.2%. In T-FEC, the values were 95.2% and 98.9%, respectively. CONCLUSIONS: These results suggest that TC6 is tolerable in Japanese, and that this regimen can also be performed in outpatient clinics. However, with the TC6 regimen, the compliance was slightly lower than with the T-FEC regimen, and supportive therapy needs to be managed appropriately.

[790]

**TÍTULO / TITLE:** - Frequent concerted genetic mechanisms disrupt multiple components of the NRF2 inhibitor KEAP1/CUL3/RBX1 E3-ubiquitin ligase complex in thyroid cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer. 2013 Oct 20;12(1):124.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1476-4598-12-124](#)

**AUTORES / AUTHORS:** - Martinez VD; Vucic EA; Pikor LA; Thu KL; Hubaux R; Lam WL

**RESUMEN / SUMMARY:** - BACKGROUND: Reactive oxygen species contribute to normal thyroid function. The NRF2 oxidative response pathway is frequently and constitutively activated in multiple tumor types, including papillary thyroid carcinoma (PTC). Genetic mechanisms underlying NRF2 pathway activation in PTC are not fully understood. Thus, we aimed to determine whether inactivating patterns of DNA-level alterations affect genes encoding for individual NRF2 inhibitor complex components (CUL3/KEAP1/RBX1) occur in PTC. FINDINGS: Combined patterns of epi/genetic alterations for KEAP1/CUL3/RBX1 E3 ubiquitin-ligase complex components were simultaneously interrogated for a panel of 310 PTC cases and 40 adjacent non-malignant tissues. Data were obtained from The Cancer Genome Atlas project. Enrichment of NRF2 pathway activation was assessed by gene-set enrichment analysis using transcriptome data. Our analyses revealed that PTC sustain a strikingly high frequency (80.6%) of disruption to multiple component genes of the NRF2 inhibitor complex. Hypermethylation is the predominant inactivating mechanism primarily affecting KEAP1 (70.6%) and CUL3 (20%), while copy number loss mostly affects RBX1 (16.8%). Concordantly, NRF2-associated gene expression signatures are positively and significantly enriched in PTC. CONCLUSIONS: The KEAP1/CUL3/RBX1 E3-ubiquitin ligase complex is almost ubiquitously affected by multiple DNA-level mechanisms and downstream NRF2 pathway targets are activated in PTC. Given the importance of this pathway to normal thyroid function as well as to cancer; targeted inhibition of NRF2 regulators may impact strategies for therapeutic intervention involving this pathway.

[791]

**TÍTULO / TITLE:** - Naturally occurring canine cancers: powerful models for stimulating pharmacogenomic advancement in human medicine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Dec;14(16):1929-31. doi: 10.2217/pgs.13.178.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.178](#)

**AUTORES / AUTHORS:** - Rotroff DM; Thomas R; Breen M; Motsinger-Reif AA

**INSTITUCIÓN / INSTITUTION:** - Bioinformatics Research Center, Department of Statistics, Bioinformatics Research Center, North Carolina State University, Raleigh, NC 27695, USA.

[792]

**TÍTULO / TITLE:** - Genetic variations in cytotoxic T-lymphocyte antigen-4 and susceptibility to cervical cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int Immunopharmacol. 2013 Nov 4;18(1):71-76. doi: 10.1016/j.intimp.2013.10.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.intimp.2013.10.018](#)

**AUTORES / AUTHORS:** - Xiong YH; He L; Fei J

**INSTITUCIÓN / INSTITUTION:** - Wuhan University Health Sciences Center, Wuhan 430071, Hubei, China; Department Of Gynecology and Obstetrics, People's Hospital of Jiangxi Province, Nanchang 330006, Jiangxi, China.

**RESUMEN / SUMMARY:** - Cytotoxic T-lymphocyte antigen-4 (CTLA-4), a molecule expressed predominantly on activated T cells, plays an important role in the down-regulation of T-cell activation. To evaluate the potential effects of CTLA-4 gene polymorphisms on susceptibility to cervical cancer, we genotyped polymorphisms in CTLA-4 (- 318 T/C, CT60 G/A,+49 G/A, - 658 T/C, and - 1661 G/A) and calculated odds ratios for the genotype and allele distributions between patients and controls. We then examined the functional relevance of the polymorphisms using enzyme-linked immunosorbent assays (ELISAs), in vitro lymphocyte proliferation assay, and cytotoxic assay. The CTLA-4 - 318 CC, CT60 AA, and+49 GG genotype frequencies were lower in patients than in controls (p <0.05). The frequencies of CTLA-4 - 318 T allele and CT60G allele carriers were significantly higher in patients than in controls (p <0.05). Upon stimulation, peripheral blood mononuclear cells (PBMCs) carrying the - 318TT and CT60GG genotypes exhibited significantly lower proliferation, IL-2, and IL-4 levels; fewer cytolytic activities; and higher TGF-beta levels compared with PBMCs carrying the - 318 CC/CT or CT60 AA/AG genotypes. We also found that CTLA-4 - 318 T/C and CT60 G/A single nucleotide polymorphisms were associated with the severity of cervical cancer. These results indicate that CTLA-4 - 318 T/C and CT60 G/A can affect cervical cancer susceptibility by altering the immune status of an individual.

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[793]

**TÍTULO / TITLE:** - VEGF pathway polymorphisms as prognostic and pharmacogenetic factors in cancer: a 2013 update.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Oct;14(13):1659-67. doi: 10.2217/pgs.13.165.

- Enlace al texto completo (gratis o de pago) [2217/pgs.13.165](#)

**AUTORES / AUTHORS:** - Eng L; Liu G

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Hospital/University of Toronto, Toronto, ON, Canada.

**RESUMEN / SUMMARY:** - With the recent advances in genomic medicine and the development of targeted antiangiogenic therapy for cancer patients, there has been an increased interest in the role of predictive and prognostic markers for antiangiogenic therapy. Here, we provide a summary of the angiogenesis pathway, the role of predictive and prognostic markers in cancer and a summary of the current literature and studies on predictive and prognostic markers for antiangiogenic therapy. Our aim is to summarize those studies that are currently in the literature with an emphasis on the future directions of the field from 2013 and beyond. We conclude by providing our perspective on the future directions of this growing field, as well as possible challenges and pitfalls along the way.

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[794]

**TÍTULO / TITLE:** - Developments of Polo-like Kinase 1 (Plk1) Inhibitors as Anti-Cancer Agents.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mini Rev Med Chem. 2013 Oct 25.

**AUTORES / AUTHORS:** - Li S; Zhang Y; Xu W

**INSTITUCIÓN / INSTITUTION:** - Department of Medicinal Chemistry, School of Pharmacy, Shandong University, Ji'nan, Shandong, 250012, China.  
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**RESUMEN / SUMMARY:** - Polo-like kinases (Plks) are a family of serine/threonine kinases with a highly conserved N-terminal Ser/Thr kinase catalytic domain and a C-terminal region that play crucial roles in cell cycle progression. Plk1, playing a key role in multiple steps of mitotic progression, is the most studied member of the family. It is overexpressed in a wide spectrum of cancer types and is a promising target in oncology. Most of Plk1 inhibitors competitively bind to the ATP-binding site, which is characterized with unique features. Other inhibitors target regions outside the ATP pocket. In this review some pre-clinical or clinical Plk1 inhibitors are reported, focusing on SAR studies and biological activities, including the kinase activity, in vitro and in vivo anti-tumor efficacy. Those studies exhibited the inhibitors' significant therapeutic effects. Moreover, combination therapies of these Plk1 inhibitors with other anticancer drugs resulted with synergistic effects.

[795]

**TÍTULO / TITLE:** - p27 and BCL2 expression predicts response to chemotherapy in head and neck squamous cell carcinomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oral Oncol. 2013 Nov 13. pii: S1368-8375(13)00739-2. doi: 10.1016/j.oraloncology.2013.10.018.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1016/j.oraloncology.2013.10.018](http://1016/j.oraloncology.2013.10.018)

**AUTORES / AUTHORS:** - Moreno-Galindo C; Hermsen M; Garcia-Pedrero JM; Fresno MF; Suarez C; Rodrigo JP

**INSTITUCIÓN / INSTITUTION:** - Department of Otolaryngology, Hospital Universitario Central de Asturias, University of Oviedo, Instituto Universitario de Oncología, Oviedo, España.

**RESUMEN / SUMMARY:** - OBJECTIVES: Head and neck squamous cell carcinomas (HNSCCs) are characterized by marked heterogeneity in their biological behavior and response to treatment. Our goal was the identification of biomarkers that can be used to predict response to chemotherapy in these patients. MATERIALS AND METHODS: The expression of EGFR, p53, Cyclin D1, p16, p21, p27, p-AKT, HIF-1alpha, Caspase 3 and BCL2 was analyzed by immunohistochemistry in 41 primary laryngeal/hypopharyngeal squamous cell carcinomas of patients that received induction chemotherapy (cisplatin and 5-fluorouracil) as part of their treatment. RESULTS: Positive expression of p27 and BCL2 had a significant predictive value for chemotherapy response in univariate analysis. The combination of both proteins was not superior in predicting the response to chemotherapy. Furthermore, p27 expression was the only significant predictor of chemotherapy response in multivariate analysis

(P=0.015). CONCLUSION: p27 Expression may serve as predictive biomarker of response to induction chemotherapy in HNSCC patients.

[796]

**TÍTULO / TITLE:** - Aromatase Inhibitor Associated Musculoskeletal Symptoms are associated with Reduced Physical Activity among Breast Cancer Survivors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Breast J. 2013 Oct 25. doi: 10.1111/tbj.12202.

●● Enlace al texto completo (gratis o de pago) [1111/tbj.12202](#)

**AUTORES / AUTHORS:** - Brown JC; Mao JJ; Stricker C; Hwang WT; Tan KS; Schmitz KH

**INSTITUCIÓN / INSTITUTION:** - Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

**RESUMEN / SUMMARY:** - Physical activity (PA) has numerous health benefits for breast cancer survivors. Recent data suggest that some breast cancer survivors treated with aromatase inhibitors may experience aromatase inhibitor associated musculoskeletal symptoms. It is unknown whether aromatase inhibitor associated musculoskeletal symptoms are associated with reduced PA and what other risk factors are associated with such PA reductions. We conducted a cross-sectional study at a large university-based breast cancer clinic among breast cancer survivors prescribed an aromatase inhibitor. At routine follow-up, we surveyed participants about aromatase inhibitor associated musculoskeletal symptoms, as well as pre-aromatase inhibitor, and current, PA levels. Among 300 participants, 90 (30%) reported a reduction of PA since the initiation of aromatase inhibitor therapy. Those with aromatase inhibitor associated musculoskeletal symptoms were more likely to report decreased PA (62% versus 38%,  $p = 0.001$ ) compared with those without aromatase inhibitor associated musculoskeletal symptoms. In multivariate analyses, aromatase inhibitor associated musculoskeletal symptoms (odds ratio [OR] = 2.29 [95% confidence interval [CI]: 1.36-3.86]), and body mass index (OR = 1.06 [95% CI: 1.02-1.12]) were associated with reductions in PA. In subgroup analysis among breast cancer survivors with aromatase inhibitor associated musculoskeletal symptoms, self-reported lower extremity joint pain (OR = 1.23 [95% CI: 1.00-1.50]) and impaired lower extremity physical function (OR = 1.07 [95% CI: 1.01-1.14]) were associated with reductions in PA. Breast cancer survivors with aromatase inhibitor associated musculoskeletal symptoms were more likely to report reductions in PA since initiating aromatase inhibitor therapy compared with those without aromatase inhibitor associated musculoskeletal symptoms. Our findings suggest that tailored interventions targeting lower extremity functional limitations are needed to enable breast cancer survivors with aromatase inhibitor associated musculoskeletal symptoms to participate in PA.

[797]

**TÍTULO / TITLE:** - Single Nucleotide Polymorphisms in MicroRNA Binding Sites of Oncogenes: Implications in Cancer and Pharmacogenomics.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - OMICS. 2013 Nov 28.

●● Enlace al texto completo (gratis o de pago) [1089/omi.2013.0098](#)

**AUTORES / AUTHORS:** - Manikandan M; Munirajan AK

**INSTITUCIÓN / INSTITUTION:** - Department of Genetics, Dr. ALM PG Institute of Basic Medical Sciences, University of Madras , Taramani Campus, Chennai, Tamil Nadu, India .

**RESUMEN / SUMMARY:** - Abstract Cancer, a complex genetic disease involving uncontrolled cell proliferation, is caused by inactivation of tumor suppressor genes and activation of oncogenes. A vast majority of these cancer causing genes are known targets of microRNAs (miRNAs) that bind to complementary sequences in 3' untranslated regions (UTR) of messenger RNAs and repress them from translation. Single Nucleotide Polymorphisms (SNPs) occurring naturally in such miRNA binding regions can alter the miRNA:mRNA interaction and can significantly affect gene expression. We hypothesized that 3'UTR SNPs in miRNA binding sites of proto-oncogenes could abrogate their post-transcriptional regulation, resulting in overexpression of oncogenic proteins, tumor initiation, progression, and modulation of drug response in cancer patients. Therefore, we developed a systematic computational pipeline that integrates data from well-established databases, followed stringent selection criteria and identified a panel of 30 high-confidence SNPs that may impair miRNA target sites in the 3' UTR of 54 mRNA transcripts of 24 proto-oncogenes. Further, 8 SNPs amidst them had the potential to determine therapeutic outcome in cancer patients. Functional annotation suggested that altogether these SNPs occur in proto-oncogenes enriched for kinase activities. We provide detailed in silico evidence for the functional effect of these candidate SNPs in various types of cancer.

[798]

**TÍTULO / TITLE:** - Concordance of genotype for polymorphisms in DNA isolated from peripheral blood and colorectal cancer tumor samples.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Dec;14(16):2005-12. doi: 10.2217/pgs.13.169.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.169](#)

**AUTORES / AUTHORS:** - van Huis-Tanja L; Kweekel D; Gelderblom H; Koopman M; Punt K; Guchelaar HJ; van der Straaten T

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology (K-1-P), Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, The Netherlands.

**RESUMEN / SUMMARY:** - Background & aim: Results from different pharmacogenetic association studies in colorectal cancer are often conflicting. Both peripheral blood and formalin-fixed, paraffin-embedded (FFPE) tissue are routinely used as DNA source. This could cause bias due to somatic alterations in tumor tissue, such as loss of heterozygosity. We therefore compared genotypes in DNA from peripheral blood and FFPE colorectal tumor samples for SNPs with putative influence on the cytotoxicity of chemotherapy. Materials & methods: Eleven SNPs in nine genes involved in anticancer drug metabolism or efficacy were determined in matched samples from blood and FFPE tissue of colorectal tumors by pyrosequencing and TaqMan(®) techniques. The kappa-statistic was calculated to assess concordance. Results: A total of 149 paired FFPE tissue and EDTA blood DNA samples were available for comparison. Overall, 20 out of 1418 genotypes were discordant (1.4%); in ten cases, loss of heterozygosity could not be ruled out. Only GSTP1 showed significant discordance between FFPE

tissue and blood genotype ( $\kappa = 0.947$ ; 95% CI: 0.896-0.998). Conclusion: FFPE tissue-derived DNA can be used as a valid proxy for germline DNA for a selection of SNPs in (retrospective) pharmacogenetic association studies in colorectal cancer. However, for future studies, genotyping of blood-derived DNA is preferred. Original submitted 29 May 2013; Revision submitted 23 August 2013.

[799]

**TÍTULO / TITLE:** - Positive ALDH1A3 and Negative GPX3 Expressions Are Biomarkers for Poor Prognosis of Gallbladder Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dis Markers. 2013;35(3):163-72. doi: 10.1155/2013/187043. Epub 2013 Aug 25.

●● Enlace al texto completo (gratis o de pago) [1155/2013/187043](#)

**AUTORES / AUTHORS:** - Yang ZL; Yang L; Zou Q; Yuan Y; Li J; Liang L; Zeng G; Chen S

**INSTITUCIÓN / INSTITUTION:** - Research Laboratory of Hepatobiliary Diseases, Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China.

**RESUMEN / SUMMARY:** - Background. Gallbladder cancers (GBCs) are highly aggressive cancers with high mortality. However, biological markers for the progression and prognosis of GBC are currently unavailable in the clinic. Objective. To identify biomarkers for predicting GBC metastasis and prognosis. Methods. We examined ALDH1A3 and GPX3 expressions in 46 squamous cell/adenosquamous carcinomas (SC/ASC) and 80 adenocarcinomas (AC) by using immunohistochemistry. Results. Positive ALDH1A3 and negative GPX3 expressions were significantly associated with lymph node metastasis and invasion of SC/ASCs and ACs. Univariate Kaplan-Meier analysis showed that either positive ALDH1A3 ( $P < 0.001$ ) or negative GPX3 ( $P < 0.001$ ) expression significantly correlated with decreased overall survival in both SC/ASC and AC patients. Multivariate Cox regression analysis showed that positive ALDH1A3 expression or negative GPX3 expression was an independent poor-prognostic predictor in both SC/ASC and AC patients. Conclusions. Our study suggested that positive ALDH1A3 and negative GPX3 expressions are closely associated with clinical pathological behaviors and poor prognosis of gallbladder cancer.

[800]

**TÍTULO / TITLE:** - Molecular Predictors of Sensitivity to the Insulin-like Growth Factor 1 Receptor Inhibitor Figitumumab (CP-751,871).

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 22.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0442-T](#)

**AUTORES / AUTHORS:** - Pavlicek A; Lira ME; Lee NV; Ching KA; Ye J; Cao J; Garza SJ; Hook KE; Ozeck M; Shi ST; Yuan J; Zheng X; Rejto PA; Kan JL; Christensen JG

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: 1Computational Biology, Oncology Research Unit; 2Translational Research, Oncology Research Unit; and 3Global Preclinical Statistics, Pfizer Oncology, La Jolla, California.

**RESUMEN / SUMMARY:** - Figitumumab (CP-751,871), a potent and fully human monoclonal anti-insulin-like growth factor 1 receptor (IGF1R) antibody, has been investigated in clinical trials of several solid tumors. To identify biomarkers of sensitivity and resistance to figitumumab, its in vitro antiproliferative activity was analyzed in a panel of 93 cancer cell lines by combining in vitro screens with extensive molecular profiling of genomic aberrations. Overall response was bimodal and the majority of cell lines were resistant to figitumumab. Nine of 15 sensitive cell lines were derived from colon cancers. Correlations between genomic characteristics of cancer cell lines with figitumumab antiproliferative activity revealed that components of the IGF pathway, including IRS2 (insulin receptor substrate 2) and IGFBP5 (IGF-binding protein 5), played a pivotal role in determining the sensitivity of tumors to single-agent figitumumab. Tissue-specific differences among the top predictive genes highlight the need for tumor-specific patient selection strategies. For the first time, we report that alteration or expression of the MYB oncogene is associated with sensitivity to IGF1R inhibitors. MYB is dysregulated in hematologic and epithelial tumors, and IGF1R inhibition may represent a novel therapeutic opportunity. Although growth inhibitory activity with single-agent figitumumab was relatively rare, nine combinations comprising figitumumab plus chemotherapeutic agents or other targeted agents exhibited properties of synergy. Inhibitors of the ERBB family were frequently synergistic and potential biomarkers of drug synergy were identified. Several biomarkers of antiproliferative activity of figitumumab both alone and in combination with other therapies may inform the design of clinical trials evaluating IGF1R inhibitors. *Mol Cancer Ther*; 12(12); 1-11. ©2013 AACR.

[801]

**TÍTULO / TITLE:** - B7H4, HSP27 and DJ-1 molecular markers as prognostic factors in pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - *Pancreatology*. 2013 Nov-Dec;13(6):564-9. doi: 10.1016/j.pan.2013.10.005. Epub 2013 Oct 23.

●● Enlace al texto completo (gratis o de pago) [1016/j.pan.2013.10.005](#)

**AUTORES / AUTHORS:** - Tsiaousidou A; Lambropoulou M; Chatzitheoklitos E; Tripsianis G; Tsompanidou C; Simopoulos C; Tsaroucha AK

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, General Hospital 'Agios Dimitrios', Thessaloniki, Greece; 2<sup>nd</sup> Department of Surgery and Laboratory of Experimental Surgery, Faculty of Medicine, Democritus University of Thrace, Alexandroupolis, Greece. Electronic address: [natasha\\_tsia@yahoo.com](mailto:natasha_tsia@yahoo.com).

**RESUMEN / SUMMARY:** - **OBJECTIVES:** Pancreatic cancer (PC) is one of the most lethal tumors of the gastrointestinal tract. The ability to predict which patients would benefit most from surgical intervention and chemotherapy would be a great clinical tool. A large number of potential markers have been identified lately in pancreatic cancer and their clinical utilities as prognostic tools are under investigation. **METHODS:** We recruited 41 patients who had undergone radical surgical resection for PC between 2003 and 2010. To investigate the prognostic factors, we evaluated 3 possible markers: B7H4, HSP27 and DJ-1 protein expressions in the tissue specimens of these 41 patients by immunohistochemistry and analyzed the clinical and pathological features of these specimens. **RESULTS:** The expression of the three

antigens was independently associated with a negative impact of chemotherapy with gemcitabine on patient's survival. Moreover, patients who overexpressed B7H4 had worse prognosis than the ones who did not. CONCLUSIONS: B7H4, DJ-1 and HSP27 may be used in the future as prognostic markers that express resistance of pancreatic cancer patients to chemotherapy with gemcitabine.

[802]

**TÍTULO / TITLE:** - Prostate-specific antigen growth rate constant after first-line cytotoxic chemotherapy in metastatic castration-resistant prostate cancer: A monoinstitutional experience.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Urol Oncol. 2013 Nov 13. pii: S1078-1439(13)00202-0. doi: 10.1016/j.urolonc.2013.05.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.urolonc.2013.05.002](http://1016/j.urolonc.2013.05.002)

**AUTORES / AUTHORS:** - Colloca G; Venturino A; Addamo G; Ratti R; Coccorullo Z; Caltabiano G; Viale G; Guarneri D

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, "G. Borea" Hospital, Sanremo, Italy. Electronic address: [g.colloca@katamail.com](mailto:g.colloca@katamail.com).

**RESUMEN / SUMMARY:** - OBJECTIVE: Validation in clinical practice, after first-line chemotherapy (CT) of metastatic castration-resistant prostate cancer (PC), of prostate-specific antigen growth rate constant logarithm (PSA-G), calculated by a formula developed by Stein et al. in comparison with PSA decrease (PSA-D), calculated as recommended by PCWG2. PATIENTS AND METHODS: This study is a retrospective monoinstitutional assessment of PSA-G and PSA-D after 12 weeks from the beginning of first-line cytotoxic CT in 49 patients with metastatic castration-resistant PC treated from 2006 to 2011, and whose pre-CT PSA and post-CT PSA determinations have been measured at specific time points. The 12-week PSA was measured at 80 to 91 days from the beginning of CT. RESULTS: PSA-G exhibited a significant correlation with overall survival by Mann-Whitney U test and by linear regression, whereas PSA-D did only at the first test. After multivariate analysis, PSA-G was the only posttreatment measure to predict overall survival. CONCLUSION: PSA-G appears a reliable surrogate end point after first-line cytotoxic CT outside of clinical trials. A cutoff value of PSA-G post-CT higher than 2.4 could be considered suggestive for moving to another treatment.

[803]

**TÍTULO / TITLE:** - Conventional adverse features do not predict response to adjuvant chemotherapy in stage II colon cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - ANZ J Surg. 2013 Nov 14. doi: 10.1111/ans.12444.

●● Enlace al texto completo (gratis o de pago) [1111/ans.12444](http://1111/ans.12444)

**AUTORES / AUTHORS:** - Peng SL; Thomas M; Ruszkiewicz A; Hunter A; Lawrence M; Moore J

**INSTITUCIÓN / INSTITUTION:** - Colorectal Surgery Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia.

**RESUMEN / SUMMARY:** - BACKGROUND: The role of adjuvant chemotherapy in patients with stage II colon cancer is unclear. Current guidelines recommend adjuvant chemotherapy for high-risk patients, although the benefit demonstrated to date is small. Our study examined if adjuvant chemotherapy is associated with improved cancer-specific survival in high-risk patients with stage II colon cancer. METHODS: A retrospective review was performed on patients with stage II (T3-4N0M0) colon cancer in a multi-institutional database from 1999 to 2007. Additionally, histology slides were reviewed and cancer-specific survival data were obtained from the state cancer registry. Adverse features examined were perforation, obstruction, T4 disease, poor differentiation, nodal yield less than 12, lymphovascular invasion and perineural invasion. Survival analysis was performed using the Kaplan-Meier method and Cox regression. RESULTS: There were 458 patients in the study, with a median follow-up of 5.2 years. Four patients (0.8%) were lost to follow-up. There were 290 (63%) high-risk patients, defined as having at least one adverse feature. Patients who had adjuvant chemotherapy were significantly younger (median 61 years versus 72 years,  $P < 0.001$ ) but had comparable ASA score (median 2 versus 2,  $P = 0.3$ ). There was no significant survival benefit observed associated with any one factor or when grouped. In high-risk patients the 5-year cancer specific survival with adjuvant chemotherapy was 84.8% (95% CI 78.7-91.9) compared to surgery alone 92.7% (95% CI 88.5-96.1),  $P = 0.85$ ). CONCLUSION: Adjuvant chemotherapy did not significantly improve cancer-specific survival in patients with stage II colon cancer with adverse features. Other markers for selecting appropriate patients for adjuvant treatment are required.

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[804]

**TÍTULO / TITLE:** - Genotyping of Human Leukocyte Antigen (HLA) Ancestral Haplotypes as Prognostic Marker in Cancer Using PCR Analysis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1102:353-66. doi: 10.1007/978-1-62703-727-3\_18.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-727-3 18](#)

**AUTORES / AUTHORS:** - Villabona L; Andersson E; Marchesi M; Masucci GV

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology-Pathology, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden.

**RESUMEN / SUMMARY:** - The major histocompatibility complex (MHC) comprises a set of genes that are essential to immunity and surveillance against neoplastic transformation. MHC antigens not only regulate antitumor immune responses in experimental animal models but also directly correlate with survival and prognosis of patients with various types of cancers. Effective recognition of tumor cells by effector T cells may be affected by the genotype and the extent of expression of human leukocyte antigen (HLA)-peptide complexes. Therefore, MHC antigens may serve as potential biomarkers for prognosis and allow selection of cancer patients for specific therapy. We describe PCR-based method to determine the HLA genotype in healthy individuals and patients using blood and tumor tissue as DNA source.

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[805]

**TÍTULO / TITLE:** - New modulated design, docking and synthesis of carbohydrate-conjugate heterobimetallic Cu-Sn complex as potential topoisomerase II inhibitor: In vitro DNA binding, cleavage and cytotoxicity against human cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 Sep 25. pii: S0223-5234(13)00609-0. doi: 10.1016/j.ejmech.2013.09.036.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.09.036](#)

**AUTORES / AUTHORS:** - Tabassum S; Afzal M; Arjmand F

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India. Electronic address: [tsartaj62@yahoo.com](mailto:tsartaj62@yahoo.com).

**RESUMEN / SUMMARY:** - New carbohydrate-conjugate heterobimetallic complexes [C<sub>22</sub>H<sub>50</sub>N<sub>6</sub>O<sub>13</sub>CuSnCl<sub>2</sub>] (3) and [C<sub>22</sub>H<sub>58</sub>N<sub>6</sub>O<sub>17</sub>NiSnCl<sub>2</sub>] (4) were synthesized from their monometallic analogs [C<sub>22</sub>H<sub>52</sub>N<sub>6</sub>O<sub>13</sub>Cu] (1) and [C<sub>22</sub>H<sub>60</sub>N<sub>6</sub>O<sub>17</sub>Ni] (2) containing N-glycoside ligand (L). In vitro DNA binding studies of L and complexes (1-4) with CT DNA were carried out by employing various biophysical and molecular docking techniques which revealed that heterobimetallic complex 3 strongly binds to DNA in comparison to 4, monometallic complexes (1 and 2) and the free ligand. Complex 3 cleaves pBR322 DNA via hydrolytic pathway (confirmed by T4 DNA ligase assay) and inhibited Topo-II activity in a dose-dependent manner. Furthermore, complex 3 was docked into the ATPase domain of human-Topo-II in order to probe the possible mechanism of inhibition.

[806]

**TÍTULO / TITLE:** - Research Highlights: Highlights from the most important papers in pharmacogenomics and cancer chemotherapy published in 2013.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenomics. 2013 Dec;14(16):1949-51. doi: 10.2217/pgs.13.175.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.175](#)

**AUTORES / AUTHORS:** - Sugino S; Janicki PK

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Perioperative Genomics, Department of Anesthesiology, Penn State Hershey Medical Center, Penn State College of Medicine, 500 University Drive, Hershey, PA 17033-0850, USA.

[807]

**TÍTULO / TITLE:** - miR-429 Identified by Dynamic Transcriptome Analysis Is a New Candidate Biomarker for Colorectal Cancer Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - OMICS. 2013 Nov 16.

●● Enlace al texto completo (gratis o de pago) [1089/omi.2012.0132](#)

**AUTORES / AUTHORS:** - Sun Y; Shen S; Tang H; Xiang J; Peng Y; Tang A; Li N; Zhou W; Wang Z; Zhang D; Xiang B; Ge J; Li G; Wu M; Li X

**INSTITUCIÓN / INSTITUTION:** - 1 Department of Gastroenterology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China.

**RESUMEN / SUMMARY:** - Abstract Colorectal cancer (CRC) is a common malignant gastrointestinal cancer. Efforts for preventive and personalized medicine have

intensified in the last decade with attention to novel forms of biomarkers. In the present study, microRNA and genetic analyses were performed in tandem for differential transcriptome profiling between primary tumors with or without nodes or distant metastases. Serial Test Cluster (STC) analysis demonstrated that 20 genes and two microRNAs showed distinctive expression patterns associated with the tumor, node, and metastasis (TNM) stage. The selected target genes were characterized by GO and Pathway analysis. A microRNA-target gene network analysis showed that miR-429 resided in the center of the network, indicating that miR-429 might serve important roles in the development of CRC. Real-time PCR and tissue microarrays showed that miR-429 had a dynamic expression pattern during the CRC progression stage, and was significantly downregulated in stage II and stage III clinical progression. The low expression of miR-429 was correlated with poor prognosis for CRC. Taken together, miR-429 warrant further clinical translation research as a candidate biomarker for CRC prognosis. Additional downstream targets and attendant gene function also need to be discerned to design a sound critical path to personalized medicine for persons susceptible to, or diagnosed with CRC.

[808]

**TÍTULO / TITLE:** - Serum VEGF-D concentration as a biomarker of lymphangi leiomyomatosis severity and treatment response: a prospective analysis of the Multicenter International Lymphangi leiomyomatosis Efficacy of Sirolimus (MILES) trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Lancet Respir Med. 2013 Aug;1(6):445-452.

●● [Enlace al texto completo \(gratis o de pago\) 1016/S2213-2600\(13\)70090-0](#)

**AUTORES / AUTHORS:** - Young LR; Lee HS; Inoue Y; Moss J; Singer LG; Strange C; Nakata K; Barker AF; Chapman JT; Brantly ML; Stocks JM; Brown KK; Lynch JP 3rd; Goldberg HJ; Downey GP; Swigris JJ; Taveira-Dasilva AM; Krischer JP; Trapnell BC; McCormack FX

**INSTITUCIÓN / INSTITUTION:** - Divisions of Pediatric Pulmonary Medicine and Allergy, Pulmonary and Critical Care, Vanderbilt University School of Medicine, Nashville, TN, USA (L R Young MD); Pediatrics Epidemiology Center, Department of Pediatrics, University of South Florida, Tampa, FL, USA (H-S Lee PhD, Prof J P Krischer PhD); Department of Diffuse Lung Diseases and Respiratory Failure, Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan (Y Inoue MD); National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA (J Moss MD, A M Taveira-DaSilva MD); Division of Respiriology, Department of Medicine, University of Toronto, Toronto, ON, Canada (L G Singer MD); Division of Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston, SC, USA (Prof C Strange MD); Bioscience Medical Research Center, Niigata University Medical and Dental Hospital, Niigata, Japan (Prof K Nakata MD); Division of Pulmonary and Critical Care, Oregon Health and Science University, Portland, OR, USA (Prof A F Barker MD); Respiratory Institute, Cleveland Clinic Foundation, Cleveland, OH, USA (J T Chapman MD); Division of Pulmonary and Critical Care, University of Florida, Gainesville, FL, USA (Prof M L Brantly MD); University of Texas Health Science Center at Tyler, Tyler, TX, USA (Prof J M Stocks MD); Department of Medicine, National Jewish Health, Denver, CO, USA (Prof K K

Brown MD, Prof G P Downey MD, J J Swigris DO); Division of Pulmonary and Critical Care Medicine, University of California, Los Angeles, Los Angeles, CA, USA (Prof J P Lynch 3<sup>rd</sup> MD); Division of Pulmonary and Critical Care, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (H J Goldberg MD); Division of Pulmonary Biology and Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA (Prof B C Trapnell MD); and Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA (Prof B C Trapnell, Prof F X McCormack MD).

**RESUMEN / SUMMARY:** - BACKGROUND: VEGF-D is a lymphangiogenic growth factor that has a key role in tumour metastasis. Serum VEGF-D concentrations are increased in most patients with lymphangioleiomyomatosis, a rare neoplasm associated with mTOR-activating tuberous sclerosis gene mutations, lymphadenopathy, metastatic spread, and pulmonary cyst formation. We used data from the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial to assess the usefulness of serum VEGF-D concentration as a marker of severity and therapeutic response to sirolimus in patients with lymphangioleiomyomatosis. METHODS: In the MILES trial, patients with lymphangioleiomyomatosis who had forced expiratory volume in 1 second (FEV1) of 70% or less of predicted were randomly assigned (1:1) to 12 months masked treatment with sirolimus or placebo. Serum VEGF-D concentrations were measured at baseline, 6 months, and 12 months. We used a linear regression model to assess associations of baseline VEGF-D concentrations with markers of disease severity, and a linear mixed effects model to assess the associations of VEGF-D concentrations with between-group differences in clinical, physiological, and patient-reported outcomes. FINDINGS: We included 42 patients from the placebo group and 45 from the sirolimus group in our analysis. Baseline VEGF-D concentrations in individual patients varied from 0.34 ng/mL to 16.7 ng/mL. Baseline VEGF-D concentrations were higher in patients who needed supplemental oxygen than in those who did not need supplemental oxygen (1.7 ng/mL [IQR 0.99-3.36] vs 0.84 ng/mL [0.52-1.39];  $p < 0.0001$ ) and in those who had a bronchodilator response than in those who did not (2.01 ng/mL [0.99-2.86] vs 1.00 ng/mL [0.61-2.15];  $p = 0.0273$ ). Median serum VEGF-D concentrations were similar at baseline in the sirolimus and placebo groups, and fell from baseline at 6 and 12 months in the sirolimus group but remained roughly stable in the placebo group. Each one-unit increase in baseline  $\log(\text{VEGF-D})$  was associated with a between-group difference in baseline-to-12-month FEV1 change of 134 mL ( $p = 0.0007$ ). In the sirolimus group, improvement in baseline-to-12-month FEV1 occurred in 15 of 23 (65%) VEGF-D responders (ie, those in whom baseline-to-12-month VEGF-D concentrations decreased by more than they did in any patients in the placebo group) and four of 15 (27%) VEGF-D non-responders ( $p = 0.0448$ ). INTERPRETATION: Serum VEGF-D is a biologically plausible and useful biomarker in lymphangioleiomyomatosis that correlates with disease severity and treatment response. Measurement of serum VEGF-D concentrations could inform the risk-benefit analysis of sirolimus therapy in patients with lymphangioleiomyomatosis and reduce the numbers of patients needed for clinical trials.

[809]

**TÍTULO / TITLE:** - Recent Progress in the Development of Histone Deacetylase Inhibitors as Anti-Cancer Agents.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mini Rev Med Chem. 2013 Oct 25.

**AUTORES / AUTHORS:** - Zhang L; Lei J; Shan Y; Yang H; Ma Y

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, No. 277, Yanta West Road, Xi'an, Shaanxi Province, 710061, P.R. China. [mx2m3m@163.com](mailto:mx2m3m@163.com).

**RESUMEN / SUMMARY:** - Histone deacetylases (HDACs) regulate the expression and activity of many proteins in both cancer initiation and cancer progression. HDACs are now recognized as promising targets for anticancer agent development. HDAC inhibitors (HDACIs) are emerging as promising anticancer drugs which possess tumor-selective cytotoxicity. HDACIs could promote growth arrest, differentiation, and apoptosis of cancer cells, with minimal effects on normal tissue. Research of HDACIs is now becoming an interesting field. HDACIs comprise structurally diverse anticancer agents and have been widely used in clinic. This review describes recent progress in the development of HDACIs, especially focus on the design strategies, novel chemical structures, biological properties and structure-activity relationships (SARs) of HDACIs. We hope it will be helpful for medicinal chemists who are interested in discovery of anticancer agents.

[810]

**TÍTULO / TITLE:** - Wnt signaling blockage inhibits cell proliferation and migration, and induces apoptosis in triple-negative breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 Nov 4;11(1):280.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1479-5876-11-280](#)

**AUTORES / AUTHORS:** - Bilir B; Kucuk O; Moreno CS

**RESUMEN / SUMMARY:** - BACKGROUND: Triple-negative breast cancer (TNBC) is an aggressive clinical subtype of breast cancer that is characterized by the lack of estrogen receptor (ER) and progesterone receptor (PR) expression as well as human epidermal growth factor receptor 2 (HER2) overexpression. The TNBC subtype constitutes approximately 10%--20% of all breast cancers, but has no effective molecular targeted therapies. Previous meta-analysis of gene expression profiles of 587 TNBC cases from 21 studies demonstrated high expression of Wnt signaling pathway-associated genes in basal-like 2 and mesenchymal subtypes of TNBC. In this study, we investigated the potential of Wnt pathway inhibitors in effective treatment of TNBC. METHODS: Activation of Wnt pathway was assessed in four TNBC cell lines (BT-549, MDA-MB-231, HCC-1143 and HCC-1937), and the ER+ cell line MCF-7 using confocal microscopy and Western blot analysis of pathway components. Effectiveness of five different Wnt pathway inhibitors (iCRT-3, iCRT-5, iCRT-14, IWP-4 and XAV-939) on cell proliferation and apoptosis were tested in vitro. The inhibitory effects of iCRT-3 on canonical Wnt signaling in TNBC was evaluated by quantitative real-time RT-PCR analysis of Axin2 and dual-luciferase reporter assays. The effects of shRNA knockdown of SOX4 in combination with iCRT-3 and genistein treatments on cell proliferation, migration and invasion on BT-549 cells were also evaluated. RESULTS: Immunofluorescence staining of beta-catenin in TNBC cell lines showed both nuclear and cytoplasmic localization, indicating activation of Wnt pathway in TNBC cells. iCRT-3 was the most effective compound for inhibiting proliferation and antagonizing Wnt signaling in TNBC cells. In addition, treatment with iCRT-3 resulted in increased

apoptosis in vitro. Knockdown of the Wnt pathway transcription factor, SOX4 in triple negative BT-549 cells resulted in decreased cell proliferation and migration, and combination treatment of iCRT-3 with SOX4 knockdown had a synergistic effect on inhibition of cell proliferation and induction of apoptosis. CONCLUSIONS: These data suggest that targeting SOX4 and/or the Wnt pathway could have therapeutic benefit for TNBC patients.

[811]

**TÍTULO / TITLE:** - Targeting sphingosine kinase induces apoptosis and tumor regression for KSHV-associated primary effusion lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Oct 18.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1535-7163.MCT-13-](#)

[0466](#)

**AUTORES / AUTHORS:** - Qin Z; Dai L; Trillo-Tinoco J; Senkal C; Wang W; Reske T; Bonstaff K; Del Valle L; Rodriguez P; Flemington E; Voelkel-Johnson C; Smith CD; Ogretmen B; Parsons C

**INSTITUCIÓN / INSTITUTION:** - 1Microbiology, Louisiana State University Health Sciences Center.

**RESUMEN / SUMMARY:** - Sphingosine kinase (SphK) is overexpressed by a variety of cancers, and its phosphorylation of sphingosine results in accumulation of sphingosine-1-phosphate (S1P) and activation of anti-apoptotic signal transduction. Existing data indicate a role for S1P in viral pathogenesis, but roles for SphK and S1P in virus-associated cancer progression have not been defined. Rare pathologic variants of diffuse large B-cell lymphoma arise preferentially in the setting of HIV infection, including primary effusion lymphoma (PEL), a highly mortal tumor etiologically linked to the Kaposi's sarcoma-associated herpesvirus (KSHV). We have found that ABC294640, a novel clinical-grade small molecule selectively targeting SphK (SphK2 >> SphK1), induces dose-dependent caspase cleavage and apoptosis for KSHV+ patient-derived PEL cells, in part through inhibition of constitutive signal transduction associated with PEL cell proliferation and survival. These results were validated with induction of PEL cell apoptosis using SphK2-specific siRNA, as well as confirmation of drug-induced SphK inhibition in PEL cells with dose-dependent accumulation of pro-apoptotic ceramides and reduction of intracellular S1P. Furthermore, we demonstrate that systemic administration of ABC294640 induces tumor regression in an established human PEL xenograft model. Complimentary ex vivo analyses revealed suppression of signal transduction and increased KSHV lytic gene expression within drug-treated tumors, with the latter validated in vitro through demonstration of dose-dependent viral lytic gene expression within PEL cells exposed to ABC294640. Collectively, these results implicate interrelated mechanisms and SphK2 inhibition in the induction of PEL cell death by ABC294640 and rationalize evaluation of ABC294640 in clinical trials for the treatment of KSHV-associated lymphoma.

[812]

**TÍTULO / TITLE:** - Evaluating the 21-gene assay Recurrence Score as a predictor of clinical response to 24 weeks of neoadjuvant exemestane in estrogen receptor-positive breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Clin Oncol. 2013 Oct 8.

- [Enlace al texto completo \(gratis o de pago\) 1007/s10147-013-0614-x](#)

**AUTORES / AUTHORS:** - Ueno T; Masuda N; Yamanaka T; Saji S; Kuroi K; Sato N; Takei H; Yamamoto Y; Ohno S; Yamashita H; Hisamatsu K; Aogi K; Iwata H; Sasano H; Toi M

**INSTITUCIÓN / INSTITUTION:** - Department of Breast Surgery, Graduate School of Medicine, Kyoto University, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: The aim of this study was to investigate the association between the results of the Recurrence Score (RS) assay and the clinical response to neoadjuvant endocrine therapy in postmenopausal women with breast cancer. METHODS: Core biopsy samples at baseline and post-treatment surgical samples were obtained from 80 and 77 of 116 patients, respectively, enrolled in the multicenter prospective study of neoadjuvant exemestane therapy (JFMC34-0601). The 21-gene assay was performed after appropriate manual microdissection. The estrogen receptor (ER), progesterone receptor, HER2 and Ki-67 were assayed by immunohistochemistry at a central laboratory. Clinical response was assessed based on the RECIST (Response Evaluation Criteria In Solid Tumors) guideline. RESULTS: Sixty-four core biopsy samples and 52 resection samples met the RS quality requirements. The clinical response rate in those patients with a low RS result (low RS group; 19/32, 59.4 %) was significantly higher than that in those patients with a high RS result (high RS group; 3/15, 20.0 %) (P = 0.015) and similar to that in patients with an intermediate RS result (intermediate RS group; 10/17, 58.8 %). The rates of breast-conserving surgery (BCS) were 90.6 % (29/32) in the low RS group, 76.5 % (13/17) in the intermediate RS group and 46.7 % (7/15) in the high RS group. The odds ratio for BCS adjusted for continuous baseline Ki-67 was 0.114 [95 % confidence interval (CI) 0.014-0.721; P = 0.028] between the high and low RS groups. RS values in pre-treatment samples were highly correlated with those in post-treatment samples (Spearman correlation coefficient 0.745, 95 % CI 0.592-0.846). CONCLUSION: Our results demonstrate the predictive value of the RS for clinical response to neoadjuvant exemestane therapy in postmenopausal women with ER-positive breast cancer.

[813]

**TÍTULO / TITLE:** - Tocilizumab in patients with active rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs or tumor necrosis factor inhibitors: Subanalysis of Spanish results of an open-label study close to clinical practice.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Reumatol Clin. 2013 Oct 4. pii: S1699-258X(13)00149-6. doi: 10.1016/j.reuma.2013.07.002.

- [Enlace al texto completo \(gratis o de pago\) 1016/j.reuma.2013.07.002](#)

**AUTORES / AUTHORS:** - Alvaro-Gracia JM; Fernandez-Nebro A; Garcia-Lopez A; Guzman M; Blanco FJ; Navarro FJ; Bustabad S; Armendariz Y; Roman-Ivorra JA

**INSTITUCIÓN / INSTITUTION:** - Servicio de Reumatología, Unidad de Terapias Biológicas, Hospital Universitario de La Princesa, Madrid, España. Electronic address: [jalvarogracia@gmail.com](mailto:jalvarogracia@gmail.com).

**RESUMEN / SUMMARY:** - OBJECTIVES: To analyze the Spanish experience in an international study which evaluated tocilizumab in patients with rheumatoid arthritis (RA) and an inadequate response to conventional disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor inhibitors (TNFi) in a clinical practice setting. MATERIAL AND METHODS: Subanalysis of 170 patients with RA from España who participated in a phase IIIb, open-label, international clinical trial. Patients presented inadequate response to DMARDs or TNFi. They received 8mg/kg of tocilizumab every 4 weeks in combination with a DMARD or as monotherapy during 20 weeks. Safety and efficacy of tocilizumab were analyzed. Special emphasis was placed on differences between failure to a DMARD or to a TNFi and the need to switch to tocilizumab with or without a washout period in patients who had previously received TNFi. RESULTS: The most common adverse events were infections (25%), increased total cholesterol (38%) and transaminases (15%). Five patients discontinued the study due to an adverse event. After six months of tocilizumab treatment, 71/50/30% of patients had ACR 20/50/70 responses, respectively. A higher proportion of TNFi-naive patients presented an ACR20 response: 76% compared to 64% in the TNFi group with previous washout and 66% in the TNFi group without previous washout. CONCLUSIONS: Safety results were consistent with previous results in patients with RA and an inadequate response to DMARDs or TNFi. Tocilizumab is more effective in patients who did not respond to conventional DMARDs than in patients who did not respond to TNFi.

[814]

**TÍTULO / TITLE:** - Overexpression of melanoma-associated antigen D4 is an independent prognostic factor in squamous cell carcinoma of the esophagus.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dis Esophagus. 2013 Oct 21. doi: 10.1111/dote.12156.

●● Enlace al texto completo (gratis o de pago) [1111/dote.12156](#)

**AUTORES / AUTHORS:** - Oya H; Kanda M; Takami H; Hibino S; Shimizu D; Niwa Y; Koike M; Nomoto S; Yamada S; Nishikawa Y; Asai M; Fujii T; Nakayama G; Sugimoto H; Fujiwara M; Kodera Y

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Nagoya, Japan.

**RESUMEN / SUMMARY:** - To pursue an urgently needed treatment target for esophageal cancer (EC), we investigated the function of the recently discovered melanoma-associated antigen (MAGE)-D4 in squamous cell EC. MAGE-D4 messenger RNA (mRNA) expression was analyzed in nine EC cell lines using quantitative reverse transcription polymerase chain reaction. In 65 surgical specimens of squamous cell EC with no prior neoadjuvant therapy, MAGE-D4 mRNA expression in EC tissues and corresponding normal tissues was analyzed and compared, and evaluated in terms of clinicopathological factors. In representative cases, MAGE-D4 protein distribution was analyzed immunohistochemically. The heterogeneity of MAGE-D4 mRNA expression was confirmed in EC cell lines by quantitative reverse transcription polymerase chain reaction. In surgical specimens, MAGE-D4 mRNA expression was significantly higher in EC tissues than in corresponding normal tissues

( $P < 0.001$ ). Patients with the highest MAGE-D4 mRNA expression in EC tissues (top quartile,  $n = 17$ ) had significantly shorter overall survival than patients with low expression (2-year survival: 44% and 73%, respectively,  $P = 0.006$ ). Univariate analysis identified age ( $\geq 65$  years), lymphatic involvement, and high MAGE-D4 mRNA expression as significant prognostic factors; high MAGE-D4 mRNA expression was also an independent prognostic factor in multivariable analysis (hazard ratio: 2.194;  $P = 0.039$ ) and was significantly associated with Brinkman index ( $P = 0.008$ ) and preoperative carcinoembryonic antigen level ( $P = 0.002$ ). Immunohistochemical MAGE-D4b expression was consistent with MAGE-D4 mRNA profiling. Our results suggest that MAGE-D4 overexpression influences tumor progression, and MAGE-D4 can be a prognostic marker and a potential molecular target in squamous cell EC.

[815]

**TÍTULO / TITLE:** - Effectiveness and cost-effectiveness of erlotinib versus gefitinib in first-line treatment of epidermal growth factor receptor-activating mutation-positive non-small-cell lung cancer patients in Hong Kong.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Hong Kong Med J. 2013 Nov 22. doi: 10.12809/hkmj133986.

●● [Enlace al texto completo \(gratis o de pago\) 12809/hkmj133986](#)

**AUTORES / AUTHORS:** - Lee VW; Schwander B; Lee VH

**INSTITUCIÓN / INSTITUTION:** - School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong.

**RESUMEN / SUMMARY:** - **OBJECTIVE.** To compare the effectiveness and cost-effectiveness of erlotinib versus gefitinib as first-line treatment of epidermal growth factor receptor-activating mutation-positive non-small-cell lung cancer patients. **DESIGN.** Indirect treatment comparison and a cost-effectiveness assessment. **SETTING.** Hong Kong. **PATIENTS.** Those having epidermal growth factor receptor-activating mutation-positive non-small-cell lung cancer. **INTERVENTIONS.** Erlotinib versus gefitinib use was compared on the basis of four relevant Asian phase-III randomised controlled trials: one for erlotinib (OPTIMAL) and three for gefitinib (IPASS; NEJGSG; WJTOG). The cost-effectiveness assessment model simulates the transition between the health states: progression-free survival, progression and death, over a lifetime horizon. The World Health Organization criterion (incremental cost-effectiveness ratio  $< 3$  times of gross domestic product/capita:  $< US\$102\,582$ ; approximately  $< HK\$798\,078$ ) was used to rate cost-effectiveness. **RESULTS.** The best fit of study characteristics and prognostic patient characteristics were found between the OPTIMAL and IPASS trials. Comparing progression-free survival hazard ratios of erlotinib versus gefitinib using only these randomised controlled trials in an indirect treatment comparison resulted in a statistically significant progression-free survival difference in favour of erlotinib (indirect treatment comparison hazard ratio=0.33; 95% confidence interval, 0.19-0.58;  $P=0.0001$ ). The cost-effectiveness assessment model showed that the cost per progression-free life year gained and per quality-adjusted life year gained was at acceptable values of US\$39 431 (approximately HK\$306 773) and US\$62 419 (approximately HK\$485 619) for erlotinib versus gefitinib, respectively. **CONCLUSION.** The indirect treatment comparison of OPTIMAL versus IPASS shows that erlotinib is significantly more efficacious than gefitinib. Furthermore, the cost-effectiveness assessment indicates that the incremental cost-effectiveness ratios are

well within an acceptable range in relation to the survival benefits obtained. In conclusion, erlotinib is cost-effective compared to gefitinib for first-line epidermal growth factor receptor-activating mutation-positive non-small-cell lung cancer patients.

[816]

**TÍTULO / TITLE:** - Emerging tyrosine kinase inhibitors for head and neck cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Emerg Drugs. 2013 Dec;18(4):445-59. doi: 10.1517/14728214.2013.842976. Epub 2013 Oct 5.

●● Enlace al texto completo (gratis o de pago) [1517/14728214.2013.842976](https://doi.org/10.1517/14728214.2013.842976)

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**RESUMEN / SUMMARY:** - Introduction: Conventional treatments for head and neck squamous cell cancer (HNSCC) are not completely effective and present several issues in terms of toxicity. Treatments available consist of surgery, chemoradiotherapy and biological agents. Areas covered: Tyrosine-kinase inhibitors (TKIs) alone or in combination, already tested or currently under investigation, will be evaluated together with their time placement along the treatment as well as the disease setting where they were used. Expert opinion: From the results of the main trials on TKIs, it emerges that these agents added to chemotherapy in recurrent/metastatic setting do not represent the best approach because of the major side effects, worsened by the complex characteristics of treated patients, and the lack of gain in terms of efficacy. Targeted agents could better exploit their activity in other settings, such as either before local regional treatment or immediately after to modulate biological effects induced by the treatment itself (surgery and/or radiation) and/or concurrently with radiation. Future research should also focus on irreversible pan-HER inhibitors, or combination agents able to overcome primary and acquired resistance, and on relevant biomarkers that would allow for a better therapeutic index of these molecules.

[817]

**TÍTULO / TITLE:** - New diarylamides and diarylureas possessing 8-amino(acetamido)quinoline scaffold: Synthesis, antiproliferative activities against melanoma cell lines, kinase inhibition, and in silico studies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Eur J Med Chem. 2013 Aug 9;70C:10-21. doi: 10.1016/j.ejmech.2013.06.060.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.06.060](https://doi.org/10.1016/j.ejmech.2013.06.060)

**AUTORES / AUTHORS:** - Koh EJ; El-Gamal MI; Oh CH; Lee SH; Sim T; Kim G; Choi HS; Hong JH; Lee SG; Yoo KH

**INSTITUCIÓN / INSTITUTION:** - Chemical Kinomics Research Center, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea; Department of Chemistry and Nano Science (BK21), Ewha Womans University, Seoul 120-750, Republic of Korea.

**RESUMEN / SUMMARY:** - Synthesis of a new series of diarylureas and diarylamides possessing 4-aryl-8-amino(acetamido)quinoline scaffold is described. Their in vitro antiproliferative activities against ten melanoma cell lines were tested. Compounds 1l, 2l, 3c, and 4c showed the highest potency against A375P cell line with IC50 values in sub-micromolar scale. Compound 4c was equipotent to Vemurafenib against A375P. In addition, compounds 1l, 2a, and 2l showed high potency over the NCI-9 tested melanoma cell line panel. The IC50 values of compounds 1l and 2l were in 2-digit nanomolar scale over four and five cell lines, respectively. Compound 2l showed high, dose-dependent inhibition of ERK kinase. ADME profiling showed that compounds 1l, 2l, 3c, 4c, and 5b are estimated to be orally bioavailable.

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[818]

**TÍTULO / TITLE:** - A new bisphosphonate derivative, CP, induces gastric cancer cell apoptosis via activation of the ERK1/2 signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Acta Pharmacol Sin. 2013 Nov 18. doi: 10.1038/aps.2013.103.

●● Enlace al texto completo (gratis o de pago) [1038/aps.2013.103](#)

**AUTORES / AUTHORS:** - Wang HJ; Liu Y; Fan LQ; Han CL; Jiang Y; Cheng SJ; Li Y

**INSTITUCIÓN / INSTITUTION:** - 1] Department of Surgery, the Fourth Affiliated Hospital of Hebei Medical University, Shijiazhuang 050011, China [2] Department of Surgery, the Affiliated Hospital of Hebei University, Baoding 071000, China.

**RESUMEN / SUMMARY:** - Aim: To investigate the effects of a new derivative of bisphosphonates, [2-(6-aminopurine-9-yl)-1-hydroxy-phosphine acyl ethyl] phosphonic acid (CP), on human gastric cancer. Methods: Human gastric cancer cell lines (SGC-7901, BGC-823, MKN-45, and MKN-28) and human colon carcinoma cell lines (LoVo and HT-29) were tested. Cell growth was determined using the MTT assay. Flow cytometry, Western blot, caspase activity assay and siRNA transfection were used to examine the mechanisms of anticancer action. Female BALB/c nude mice were implanted with SGC-7901 cells. From d6 after inoculation, the animals were injected with CP (200 µg/kg, ip) or vehicle daily for 24 d. Results: CP suppressed the growth of the 6 human cancer cell lines with similar IC50 values (3239 µmol/L). In SGC-7901 cells, CP arrested cell cycle progression at the G2/M phase. The compound activated caspase-9, increased the expression of pro-apoptotic proteins Bax and Bad, decreased the expression of anti-apoptotic protein Bcl-2. Furthermore, the compound selectively activated ERK1/2 without affecting JNK and p38 in SGC-7901 cells. Treatment of SGC-7901 cells with the specific ERK1/2 inhibitor PD98059 or ERK1/2 siRNA hampered CP-mediated apoptosis. In the human gastric cancer xenograft nude mouse model, chronic administration of CP significantly retarded the tumor growth. Conclusion: CP is a broad-spectrum inhibitor of human carcinoma cells in vitro, and it also exerts significant inhibition on gastric cancer cell growth in vivo. CP induces human gastric cancer apoptosis via activation of the ERK1/2 signaling pathway.

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[819]

**TÍTULO / TITLE:** - Suppression of NF-kappaB signaling and P-glycoprotein Function by Gambogic Acid Synergistically Potentiates Adriamycin -induced Apoptosis in Lung Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Cancer Drug Targets. 2013 Nov 12.

**AUTORES / AUTHORS:** - Wang LH; Yang JY; Yang SN; Li Y; Ping GF; Hou Y; Cui W; Wang ZZ; Xiao W; Wu CF

**INSTITUCIÓN / INSTITUTION:** - 1Department of Pharmacology, Shenyang Pharmaceutical University, Shenyang, 110016, People's Republic of China.  
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**RESUMEN / SUMMARY:** - Gambogic acid (GA) has been approved by the Chinese Food and Drug Administration for the treatment of lung cancer in clinical trials. However, whether GA has chemosensitizing properties when combined with other chemotherapy agents in the treatment of lung cancer is not known. Here we investigated the effects of GA combined with adriamycin (ADM), a common chemotherapy agent, in regard to their activities and the possible mechanisms against lung cancer in vitro and in vivo. Cell viability results showed that sequential GA-ADM treatment was synergistic, while the reverse sequence and simultaneous treatments were antagonistic or additive, in lung cancer cells and ADM resistant cells, but not in normal cells. The combined use of GA and ADM synergistically displayed apoptosis-inducing activities in lung cancer cells. Moreover, GA in combination with ADM could promote PARP cleavage, enhance caspases activation and decrease the expression of anti-apoptotic proteins in lung cancer cells. The combined use of GA and ADM decreased the expression of P-glycoprotein and increased the accumulation of ADM in lung cancer cells. Furthermore, it was found that, prior to ADM treatment, GA could inhibit NF-kappaB signaling pathways, of which have been validated to confer ADM resistance. The critical role of NF-kappaB was further confirmed by using PDTC, a NF-kappaB inhibitor, which significantly increased apoptosis induction by the combination of GA and ADM and inhibited ADM-induced ABCB1 upregulation. Importantly, our results indicated that the combination of GA and ADM exerted enhanced anti-tumor effects on A549 xenograft models through inhibiting NF-kappaB and P-glycoprotein, and attenuated ADM-induced cardiotoxicity. Collectively, these findings indicate that GA sensitizes lung cancer cells to ADM in vitro and in vivo, providing a rationale for the combined use of GA and ADM in lung cancer chemotherapy.

[820]

**TÍTULO / TITLE:** - Fluorouracil and Other Predictors of Morpheiform Basal Cell Carcinoma Among High-Risk Patients: The Veterans Affairs Topical Tretinoin Chemoprevention Trial.

**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 Nov 20. doi:  
10.1001/jamadermatol.2013.5619.

●● Enlace al texto completo (gratuito o de pago)

[1001/jamadermatol.2013.5619](http://1001/jamadermatol.2013.5619)

**AUTORES / AUTHORS:** - Xiong MY; Korgavkar K; Digiovanna JJ; Weinstock MA

**INSTITUCIÓN / INSTITUTION:** - Dermatoepidemiology Unit, VA Medical Center, Providence, Rhode Island  
2Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, Rhode Island.

[821]

**TÍTULO / TITLE:** - A comparative study of affibody, panitumumab, and EGF for near-infrared fluorescence imaging of EGFR- and EGFRvIII-expressing tumors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Oct 7;15(2).

**AUTORES / AUTHORS:** - Gong H; Kovar JL; Cheung L; Rosenthal EL; Olive DM

**INSTITUCIÓN / INSTITUTION:** - LI-COR Biosciences; Lincoln, NE USA.

**RESUMEN / SUMMARY:** - Aberrant overexpression and/or activation of epidermal growth factor receptor (EGFR) is associated with many types of cancers. EGFR variant III (EGFRvIII) is a common in-frame deletion mutant, which lacks a large part of the extracellular portion (exons 2-7), including components of the ligand-binding domain. Although EGFR has been extensively studied as a molecular imaging target, information about EGFRvIII-targeted molecular imaging is lacking. In this study, the EGFR-specific affibody, therapeutic antibody panitumumab and ligand EGF were labeled with IRDye 800CW (Ex/Em: 774/789 nm), yielding Aff800, Pan800 and EGF800, respectively. The binding affinities of the labeled agents were compared in cell-based assays using a rat glioma cell line F98 parental (F98-p) lacking EGFR expression, and two F98-derived transgenic cell lines expressing EGFR or EGFRvIII (designated as F98-EGFR and F98-vIII, respectively). Results showed that all agents could bind to F98-EGFR, with Pan800 having the highest binding affinity, followed by Aff800 and EGF800. Pan800 and Aff800, but not EGF800, also bound to F98-vIII. In vivo animal imaging demonstrated that compared to F98-p tumors, F98-EGFR tumors generated higher signals with all three agents. However, in the case of F98-vIII, only Pan800 and Aff800 signals were higher. Analysis of tissue lysates showed that a large portion of Pan800 was degraded into small fragments in F98-EGFR and F98-vIII tumors, possibly due to proteolytic digestion after its specific binding and internalization. In conclusion, Pan800 and Aff800 could be used as imaging agents for both wild type EGFR and EGFRvIII, whereas EGF800 only targets wild type EGFR.

[822]

**TÍTULO / TITLE:** - Lymphatic invasion as a prognostic biomarker in primary cutaneous melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1102:275-86. doi: 10.1007/978-1-62703-727-3\_15.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-727-3\\_15](#)

**AUTORES / AUTHORS:** - Xu X; Gimotty PA; Guerry D; Karakousis G; Elder DE

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology and Laboratory Medicine, Hospital of University of Pennsylvania, Philadelphia, PA, USA.

**RESUMEN / SUMMARY:** - Melanoma has a propensity for lymph node metastasis. However, the incidence of lymphatic invasion detected by histology alone in primary melanoma is disproportionately low in comparison to the incidence of positive sentinel lymph nodes (SLN). With the discovery of lymphatic endothelial cell markers, such as podoplanin and LYVE-1, lymphatic vessels can be reliably detected in formalin-fixed paraffin-embedded (FFPE) tissues. There is a now consensus that lymphatic invasion detected by immunohistochemical stains in primary melanoma is much more common

than previously reported by histological examination alone. Immunohistochemical stains show that lymphangiogenesis and lymphatic invasion in primary melanoma may occur intratumorally or peritumorally, and lymphatic invasion is common across the range of tumor thicknesses in primary vertical growth phase (VGP) melanomas. A number of studies have shown that lymphatic invasion in primary melanoma is associated with a positive sentinel lymph node biopsy and a worse clinical outcome. Although not currently a part of the standard of care for staging of melanoma, the detection of lymphatic invasion in primary melanoma using immunohistochemical markers may be helpful in planning of therapy in some cases and may find a routine role in primary melanoma microscopic attributes in future.

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[823]

**TÍTULO / TITLE:** - The prognostic value of cyclin D1 in renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int Urol Nephrol. 2013 Nov 17.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11255-013-0602-0](#)

**AUTORES / AUTHORS:** - Lima MS; Pereira RA; Costa RS; Tucci S; Dantas M; Muglia VF; Ravinal RC; Barros-Silva GE

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Ribeirao Preto School of Medicine, University of Sao Paulo (USP), Av Bandeirantes 3900, Ribeirao Preto, Sao Paulo, 14110-000, Brazil.

**RESUMEN / SUMMARY:** - INTRODUCTION: Renal cell carcinoma (RCC) is a family of distinct tumors, and a variety of molecules have been evaluated as prognostic markers for RCC. Cyclin D1, a cell cycle regulator, is overexpressed in several primary tumors. OBJECTIVE: To evaluate cyclin D1 expression as a prognostic marker in RCC. METHOD: In total, 109 tumor specimens from patients with RCC were obtained from 2005 to 2010 at Hospital das Clinicas-Ribeirao Preto School of Medicine-USP, Brazil, and submitted to immunohistochemical analysis along with seven normal kidney tissue samples. RESULTS: All of the normal kidney samples lacked cyclin D1 immunohistochemical staining. In addition, there was lower protein expression in the papillary and chromophobe RCC samples. Patients with cyclin D1low tumors ( $\leq 30\%$  positive cells) showed worse clinical outcome ( $p = 0.03$ ), lower survival without metastasis and/or death by RCC ( $p = 0.03$ ), high nuclear grade ( $p = 0.001$ ), larger tumor size ( $p = 0.01$ ), presence of symptoms at diagnosis ( $p = 0.04$ ), necrosis ( $p = 0.004$ ) and sarcomatoid morphology ( $p = 0.04$ ). After multivariate analysis, cyclin D1 was not an independent significant factor for worse outcome; however, it improved the accuracy of the adopted prognostic system. The analysis performed for clear cell RCC alone showed similar statistical significance to that of the total cases. CONCLUSIONS: Cyclin D1 protein was overexpressed in RCC. The types of RCC appear to exhibit different immunohistochemical staining patterns for cyclin D1; high protein expression was related to good clinical outcome and to most known favorable prognostic factors. Further investigations are necessary to reveal which mechanisms lead to cyclin D1 accumulation in neoplastic cells.

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[824]

**TÍTULO / TITLE:** - Phosphoproteomic Profiling Identifies Focal Adhesion Kinase as a Mediator of Docetaxel Resistance in Castrate Resistant Prostate Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 5.

- Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0225-T](#)

**AUTORES / AUTHORS:** - Lee BY; Hochgrafe F; Lin HM; Castillo L; Wu J; Raftery MJ; Shreeve SM; Horvath LG; Daly RJ

**INSTITUCIÓN / INSTITUTION:** - 1Cancer Research Program, The Kinghorn Cancer Centre, Garvan Institute of Medical Research.

**RESUMEN / SUMMARY:** - Docetaxel remains the standard-of-care for men diagnosed with metastatic castrate resistant prostate cancer (CRPC). However, only ~50% of patients benefit from treatment and all develop Docetaxel-resistant disease. Here, we characterize global perturbations in tyrosine kinase signaling associated with Docetaxel-resistance and thereby develop a potential therapeutic strategy to reverse this phenotype. Using quantitative mass spectrometry-based phosphoproteomics, we identified that metastatic Docetaxel-resistant prostate cancer cell lines (DU145-Rx and PC3-Rx) exhibit increased phosphorylation of focal adhesion kinase (FAK) on Y397 and Y576, in comparison to parental controls (DU145 and PC3, respectively). Bioinformatic analyses identified perturbations in pathways regulating focal adhesions and the actin cytoskeleton and in protein-protein interaction networks related to these pathways in Docetaxel-resistant cells. Treatment with the FAK tyrosine kinase inhibitor (TKI) PF-00562271 reduced FAK phosphorylation in the resistant cells, but did not affect cell viability or Akt phosphorylation. Docetaxel administration reduced FAK and Akt phosphorylation, while co-treatment with PF-00562271 and Docetaxel resulted in an additive attenuation of FAK and Akt phosphorylation and overcame the chemoresistant phenotype. The enhanced efficacy of co-treatment was due to increased autophagic cell death, rather than apoptosis. These data strongly support that enhanced FAK activation mediates chemoresistance in CRPC, and identify a potential clinical niche for FAK TKIs, where co-administration with Docetaxel may be used in CRPC patients to overcome chemoresistance.

[825]

**TÍTULO / TITLE:** - Selective Disruption of Rb-Raf-1 Kinase Interaction Inhibits Pancreatic Adenocarcinoma Growth Irrespective of Gemcitabine Sensitivity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 21.

- Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-0719](#)

**AUTORES / AUTHORS:** - Trevino JG; Verma M; Singh S; Pillai S; Zhang D; Pernazza D; Sebti SM; Lawrence NJ; Centeno BA; Chellappan SP

**INSTITUCIÓN / INSTITUTION:** - Authors' Affiliations: Departments of 1Tumor Biology, 2Drug Discovery, and 3Anatomic Pathology, H. Lee Moffitt Cancer Center & Research Institute, Tampa; and 4Department of Surgery, University of Florida-Gainesville, Gainesville, Florida.

**RESUMEN / SUMMARY:** - Inactivation of the retinoblastoma (Rb) tumor suppressor protein is widespread in human cancers. Inactivation of Rb is thought to be initiated by

association with Raf-1 (C-Raf) kinase, and here we determined how RRD-251, a disruptor of the Rb-Raf-1 interaction, affects pancreatic tumor progression. Assessment of phospho-Rb levels in resected human pancreatic tumor specimens by immunohistochemistry (n = 95) showed that increased Rb phosphorylation correlated with increasing grade of resected human pancreatic adenocarcinomas (P = 0.0272), which correlated with reduced overall patient survival (P = 0.0186). To define the antitumor effects of RRD-251 (50  $\mu$ mol/L), cell-cycle analyses, senescence, cell viability, cell migration, anchorage-independent growth, angiogenic tubule formation and invasion assays were conducted on gemcitabine-sensitive and -resistant pancreatic cancer cells. RRD-251 prevented S-phase entry, induced senescence and apoptosis, and inhibited anchorage-independent growth and invasion (P < 0.01). Drug efficacy on subcutaneous and orthotopic xenograft models was tested by intraperitoneal injections of RRD-251 (50 mg/kg) alone or in combination with gemcitabine (250 mg/kg). RRD-251 significantly reduced tumor growth in vivo accompanied by reduced Rb phosphorylation and lymph node and liver metastasis (P < 0.01). Combination of RRD-251 with gemcitabine showed cooperative effect on tumor growth (P < 0.01). In conclusion, disruption of the Rb-Raf-1 interaction significantly reduces the malignant properties of pancreatic cancer cells irrespective of their gemcitabine sensitivity. Selective targeting of Rb-Raf-1 interaction might be a promising strategy targeting pancreatic cancer. Mol Cancer Ther; 12(12); 1-13. ©2013 AACR.

[826]

**TÍTULO / TITLE:** - PIM1 Kinase as a Target in Prostate Cancer: Roles in Tumorigenesis, Castration Resistance, and Docetaxel Resistance.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Cancer Drug Targets. 2013 Nov 25.

**AUTORES / AUTHORS:** - Holder SL; Abdulkadir SA

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

**RESUMEN / SUMMARY:** - PIM1 kinase is a serine/threonine kinase that has been shown to be overexpressed in multiple human malignancies, including prostate cancer. PIM1 phosphorylates multiple cellular substrates to inhibit apoptosis and promote cell cycle progression. Increased PIM1 can also facilitate genomic instability to promote neoplastic processes. PIM1 kinase is overexpressed in high-grade prostate intraepithelial neoplasia and in prostate cancer compared to normal prostatic tissue and benign prostate hyperplasia. Elevated PIM1 levels have been shown to be the direct result of oncogenic fusion proteins and active signal transduction pathways. In vitro and in vivo mouse studies indicate the PIM1 is weakly tumorigenic but synergizes dramatically when coexpressed with MYC. PIM1 kinase can also phosphorylate the androgen receptor (AR), thereby regulating AR degradation and function, including in a low androgen environment. This finding implicates PIM1 in castrate-resistant prostate cancer. Furthermore, expression of PIM1 has been shown to be increased in prostate tissue after docetaxel exposure, conferring partial resistance to docetaxel. Correlatively, decreased PIM1 levels sensitize prostate cancer cells to docetaxel treatment. Thus, PIM1 may be a target in docetaxel resistant disease. In summary, PIM1 kinase is involved in prostate tumorigenesis, castration resistance, and docetaxel

resistance. Several PIM1 kinase inhibitors have been reported and are in varied stages of drug development. PIM1 is involved multiple processes in the development and propagation of prostate cancer, thus a PIM1 kinase inhibitor may serve as an effective therapeutic agent in this prevalent disease.

[827]

**TÍTULO / TITLE:** - Quercetin: a pleiotropic kinase inhibitor against cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Treat Res. 2014;159:185-205. doi: 10.1007/978-3-642-38007-5\_11.

●● Enlace al texto completo (gratis o de pago) [1007/978-3-642-38007-5\\_11](#)

**AUTORES / AUTHORS:** - Russo GL; Russo M; Spagnuolo C; Tedesco I; Bilotto S; Iannitti R; Palumbo R

**INSTITUCIÓN / INSTITUTION:** - Istituto Scienze dell'Alimentazione, Consiglio Nazionale delle Ricerche, 83100, Avellino, Italy, [girusso@isa.cnr.it](mailto:girusso@isa.cnr.it).

**RESUMEN / SUMMARY:** - Increased consumption of fruits and vegetables can represent an easy strategy to significantly reduce the incidence of cancer. From this observation, derived mostly from epidemiological data, the new field of chemoprevention has emerged in the primary and secondary prevention of cancer. Chemoprevention is defined as the use of natural or synthetic compounds able to stop, reverse, or delay the process of tumorigenesis in its early stages. A large number of phytochemicals are potentially capable of simultaneously inhibiting and modulating several key factors regulating cell proliferation in cancer cells. Quercetin is a flavonoid possessing potential chemopreventive properties. It is a functionally pleiotropic molecule, possessing multiple intracellular targets, affecting different cell signaling processes usually altered in cancer cells, with limited toxicity on normal cells. Simultaneously targeting multiple pathways may help to kill malignant cells and slow down the onset of drug resistance. Among the different substrates triggered by quercetin, we have reviewed the ability of the molecule to inhibit protein kinases involved in deregulated cell growth in cancer cells.

[828]

**TÍTULO / TITLE:** - Selective inhibition of pancreatic ductal adenocarcinoma cell growth by the mitotic MPS1 kinase inhibitor, NMS-P715.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0324](#)

**AUTORES / AUTHORS:** - Slee RB; Grimes BR; Bansal R; Gore J; Blackburn C; Brown L; Gasaway R; Jeong J; Victorino J; March KL; Colombo R; Herbert BS; Korc M

**INSTITUCIÓN / INSTITUTION:** - 1Medical and Molecular Genetics, Indiana University.

**RESUMEN / SUMMARY:** - Most solid tumors, including pancreatic ductal adenocarcinoma (PDAC), exhibit structural and numerical chromosome instability (CIN). While often implicated as a driver of tumor progression and drug resistance, CIN also reduces cell fitness and poses a vulnerability which can be exploited therapeutically. The spindle assembly checkpoint (SAC) ensures correct chromosome-

microtubule attachment, thereby minimizing chromosome segregation errors. Many tumors exhibit up-regulation of SAC components such as MPS1, which may help contain CIN within survivable limits. Prior studies showed that MPS1 inhibition with the small molecule, NMS-P715, limits tumor growth in xenograft models. In cancer cell lines, NMS-P715 causes cell death associated with impaired SAC function and increased chromosome mis-segregation. While normal cells appeared more resistant, effects on stem cells, which are the dose-limiting toxicity of most chemotherapeutics, were not examined. Elevated expression of 70 genes (CIN70), including MPS1, provides a surrogate measure of CIN and predicts poor patient survival in multiple tumor types. Our new findings show that the degree of CIN70 up-regulation varies considerably among PDAC tumors, with higher CIN70 gene expression predictive of poor outcome. We identified a 25 gene subset (PDAC CIN25) whose over-expression was most strongly correlated with poor survival and included MPS1. In vitro, growth of human and murine PDAC cells is inhibited by NMS-P715 treatment, whereas adipose-derived human mesenchymal stem cells are relatively resistant and maintain chromosome stability upon exposure to NMS-P715. These studies suggest that NMS-P715 could have a favorable therapeutic index and warrant further investigation of MPS1 inhibition as a new PDAC treatment strategy.

[829]

**TÍTULO / TITLE:** - Proteomic strategy for probing complementary lethality of kinase inhibitors against pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Proteomics. 2013 Oct 24. doi: 10.1002/pmic.201300248.

●● Enlace al texto completo (gratis o de pago) [1002/pmic.201300248](#)

**AUTORES / AUTHORS:** - Lee JG; McKinney KQ; Mougeot JL; Bonkovsky HL; Hwang SI

**INSTITUCIÓN / INSTITUTION:** - Proteomics and Mass Spectrometry Research Laboratory, Carolinas HealthCare System, Charlotte, NC, USA.

**RESUMEN / SUMMARY:** - In the present study, proteomic analysis was performed to discover combinational molecular targets for therapy and chemoresistance by comparing differential protein expression from Panc-1 cells treated with FDA-approved drugs such as sunitinib, imatinib mesylate, dasatinib, and PD184352. A total of 4041 proteins were identified in the combined data from all of the treatment groups by nano-electrospray ultra-performance LC and MS/MS analysis. Most of the proteins with significant changes are involved in apoptosis, cytoskeletal remodeling, and epithelial-to-mesenchymal transition. These processes are associated with increased chemoresistance and progression of pancreatic cancer. Among the differentially expressed proteins, heme oxygenase-1 (HO-1) was found in the sunitinib and imatinib mesylate treatment groups, which possibly acts as a specific target for synthetic lethality in combinational treatment. HO-1 was found to play a key role in sensitizing the chemoresistant Panc-1 cell line to drug therapy. Viability was significantly decreased in Panc-1 cells cotreated with sunitinib and imatinib mesylate at low doses, compared to those treated with sunitinib or imatinib mesylate alone. The results suggest that induction of chemosensitization by manipulating specific molecular targets can potentiate synergistic chemotherapeutic effects at lower, better tolerated doses, and in turn reduce the toxicity of multidrug treatment of pancreatic cancer.

[830]

**TÍTULO / TITLE:** - The impact of baseline serum C-reactive protein and C-reactive protein kinetics on the prognosis of metastatic nasopharyngeal carcinoma patients treated with palliative chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 10;8(10):e76958. doi: 10.1371/journal.pone.0076958.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0076958](#)

**AUTORES / AUTHORS:** - Xia WX; Ye YF; Lu X; Wang L; Ke LR; Zhang HB; Roycik MD; Yang J; Shi JL; Cao KJ; Guo X; Xiang YQ

**INSTITUCIÓN / INSTITUTION:** - Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, Guangzhou, P. R. China ; State Key Laboratory of Oncology in Southern China, Guangzhou, P. R. China.

**RESUMEN / SUMMARY:** - BACKGROUND: The aim of this study was to determine whether baseline C-reactive protein (CRP) levels and CRP kinetics predict the overall survival in metastatic nasopharyngeal carcinoma (mNPC) patients. METHODS: A total of 116 mNPC patients from January 2006 to July 2011 were retrospectively reviewed. Serum CRP level was measured at baseline and thereafter at the start of each palliative chemotherapy cycle for all patients. RESULTS: Patients with higher values of baseline CRP ( $\geq 3.4$  mg/L) had significantly worse survival than those with lower baseline CRP values ( $< 3.4$  mg/L). Patients were divided into four groups according to baseline CRP and CRP kinetics: (1) patients whose CRP  $< 3.4$  mg/L and never elevated during treatment; (2) patients whose CRP  $< 3.4$  mg/L and elevated at least one time during treatment; (3) patients whose CRP  $\geq 3.4$  mg/L and normalized at least one time during treatment; and (4) patients whose CRP  $\geq 3.4$  mg/L and never normalized during treatment. The patients were further assigned to non-elevated, elevated, normalized, and non-normalized CRP groups. Overall survival rates were significantly different among the four groups, with three-year survival rates of 68%, 41%, 33%, and 0.03% for non-elevated, elevated, normalized, and non-normalized CRP groups respectively. When compared with the non-elevated group, hazard ratios of death were 1.69, 2.57, and 10.34 in the normalized, elevated, and non-normalized groups ( $P < 0.001$ ). CONCLUSIONS: Baseline CRP and CRP kinetics may be useful to predict the prognosis of metastatic NPC patients treated with palliative chemotherapy and facilitate individualized treatment. A prospective study to validate this prognostic model is still needed however.

[831]

**TÍTULO / TITLE:** - Serum peptidomic profiling identifies a minimal residual disease detection and prognostic biomarker for patients with acute leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Nov;6(5):1453-1460. Epub 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1574](#)

**AUTORES / AUTHORS:** - Song W; Wang N; Li W; Wang G; Hu J; He K; Li Y; Meng Y; Chen N; Wang S; Hu L; Xu B; Wang J; Li A; Cui J

**INSTITUCIÓN / INSTITUTION:** - Cancer Center, The First Hospital of Jilin University, Changchun, Jilin, P.R. China.

**RESUMEN / SUMMARY:** - The evaluation of minimal residual disease (MRD) in acute leukemia (AL) is currently recognized as a potential critical tool to assess the response and relapse rate of treatments. The present study investigated serum peptides from patients with AL to identify biomarkers that would be useful in providing clinical evaluations and independent prognostic information. The patterns of serum peptides from 123 patients with AL and 49 healthy controls were analyzed using matrix-assisted laser desorption/ionization-time of flight mass spectrometry. Furthermore, diagnostic models of differential peptides were established using the support vector machine (SVM) algorithm to discriminate between the AL patients and healthy controls or between the AL patients with various degrees of remission. Finally, the peptides were applied to evaluate the prognosis of the affected patients. The area under the receiver operating characteristic (ROC) curve (AUC), analyzed using the SVM algorithm to distinguish between the AL patients and healthy controls, was 0.921. The AUC of the models for distinguishing between the newly-diagnosed AL patients and those in AL-hematological complete remission (HCR) and between the AL-HCR patients from those in AL-molecular remission (MR), was 0.824 and 0.919, respectively. A short serum peptide of m/z 4625 was identified to decrease in density in parallel with an increase in the degree of remission, which was used to monitor the MRD level. The intensity of the m/z 4625 peptide was significantly correlated with a poor overall survival (OS). The m/z 4625 peptide was identified to be a partial fragment of SERPINA3. The serum peptide pattern is high in sensitivity and specificity and may be used to discriminate between AL patients with various degrees of remission. The m/z 4625 peptide may be used to monitor the MRD levels and provide independent prognostic information in patients with AL.

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[832]

**TÍTULO / TITLE:** - Antitumor Response of an ERBB2 Amplified Inflammatory Breast Carcinoma With EGFR Mutation to the EGFR-TKI Erlotinib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Breast Cancer. 2013 Sep 27. pii: S1526-8209(13)00223-1. doi: 10.1016/j.clbc.2013.09.010.

●● Enlace al texto completo (gratis o de pago) [1016/j.clbc.2013.09.010](#)

**AUTORES / AUTHORS:** - Ali SM; Alpaugh RK; Buell JK; Stephens PJ; Yu JQ; Wu H; Hiemstra CN; Miller VA; Lipson D; Palmer GA; Ross JS; Cristofanilli M

**INSTITUCIÓN / INSTITUTION:** - Department of Diagnostic Imaging, Foundation Medicine, Inc, Cambridge, MA.

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[833]

**TÍTULO / TITLE:** - Boldine induces cell cycle arrest and apoptosis in T24 human bladder cancer cell line via regulation of ERK, AKT, and GSK-3beta

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Urol Oncol. 2013 Nov 13. pii: S1078-1439(13)00076-8. doi: 10.1016/j.urolonc.2013.02.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.urolonc.2013.02.012](#)

**AUTORES / AUTHORS:** - Gerhardt D; Bertola G; Dietrich F; Figueiro F; Zanotto-Filho A; Moreira Fonseca JC; Morrone FB; Barrios CH; Battastini AM; Salbego CG

**INSTITUCIÓN / INSTITUTION:** - Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brasil. Electronic address: [danieli83@yahoo.com.br](mailto:danieli83@yahoo.com.br).

**RESUMEN / SUMMARY:** - OBJECTIVE: Bladder cancer is one of the most prevalent genitourinary malignancies. Despite active chemotherapy regimens, patients with bladder cancer suffer from a high rate of tumor recurrence. Thus, new approaches and agents to improve quality of life and survival still need to be developed. The objective of the present study was to evaluate the effect and underlying mechanisms of boldine, an aporphine alkaloid of *Peumus boldus*, on bladder cancer proliferation and cell death. METHODS: Sulforhodamine B assay, Tetrazolium reduction assay, Flow Cytometry Analysis, Ecto-5'-nucleotidase activity and Western blot assay were performed. RESULTS: The results showed that boldine was able to reduce cell viability and cell proliferation in T24 cells. In addition, boldine arrests the cell cycle at G2/M-phase and cause cell death by apoptosis. Boldine-induced inhibition of cell growth and cell cycle arrest appears to be linked to inactivation of extracellular signal-regulated kinase protein (ERK). Additionally, the efficacy of boldine in apoptosis-induced in T24 cells is correlated with modulation of AKT (inactivation) and glycogen synthase kinase-3beta (GSK-3beta) (activation) proteins. CONCLUSIONS: The present findings may, in part, explain the therapeutic effects of boldine for treatment of urinary bladder cancer.

[834]

**TÍTULO / TITLE:** - Human gastric cancer cell line SGC-7901 apoptosis induced by SFPS-B2 via a mitochondrial-mediated pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomed Mater Eng. 2014;24(1):1141-7. doi: 10.3233/BME-130914.

●● Enlace al texto completo (gratis o de pago) [3233/BME-130914](#)

**AUTORES / AUTHORS:** - Ji YB; Ji CF; Yue L

**INSTITUCIÓN / INSTITUTION:** - Engineering Research Center of Natural Anticancer Drugs, Ministry of Education, Harbin University of Commerce, Harbin, China.

**RESUMEN / SUMMARY:** - This study was to investigate the effect of Sargassum fusiforme polysaccharides (SFPS-B2) on the proliferation and apoptosis of human gastric cancer cell line SGC-7901. Cells were treated with different concentrations of SFPS-B2. MTT and flow cytometry (FCM) assays were performed to evaluate the effect of SFPS-B2 on the cell growth and apoptosis. Inverted fluorescent microscope was used to observe cell morphology. Laser scanning confocal microscope (LSCM) was used to analyze intracellular calcium ion concentration, mitochondrion permeability transition pore (MPTP) and mitochondrial membrane potential (MMP). Spectrophotometer was applied to quantify the activity of Caspase-9 and Caspase-3. FCM was used to determine the expressions of Bcl-2, Bax and cytochrome C. It was shown that SFPS-B2 inhibited the growth of SGC-7901. After the treatment for 72 h, the cell apoptosis morphology was obvious, which showed that cell protuberance and apoptotic body appeared, and the cytoplasm was concentrated; the apoptotic peak appeared and the apoptotic rate increased in a dose-dependent manner. After the treatment for 24 h, SFPS-B2 activated intracellular MPTP and decreased MMP. It also increased the activity of Caspase-9 and Caspase-3, down-regulated the expression of Bcl-2 and up-regulated the expression of Bax, induced the release of Cyt-C. SFPS-B2

induced SGC-7901 apoptosis through a mitochondrial-mediated pathway, suggesting it may be an agent for cancer treatment.

[835]

**TÍTULO / TITLE:** - Localized interleukin-12 delivery for immunotherapy of solid tumours.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cell Mol Med. 2013 Nov 19. doi: 10.1111/jcmm.12121.

●● Enlace al texto completo (gratis o de pago) [1111/jcmm.12121](#)

**AUTORES / AUTHORS:** - Wei LZ; Xu Y; E Nelles M; Furlonger C; Wang JC; Di Grappa MA; Khokha R; Medin JA; Paige CJ

**INSTITUCIÓN / INSTITUTION:** - Department of Immunology, University of Toronto, Toronto, ON, Canada; Ontario Cancer Institute, University Health Network, Toronto, ON, Canada.

**RESUMEN / SUMMARY:** - Interleukin (IL)-12 is the key cytokine in the initiation of a Th1 response and has shown promise as an anti-cancer agent; however, clinical trials involving IL-12 have been unsuccessful due to toxic side-effects. To address this issue, lentiviral vectors were used to transduce tumour cell lines that were injected as an autologous tumour cell vaccine. The focus of the current study was to test the efficacy of this approach in a solid tumour model. SCCVII cells that were transduced to produce IL-12 at different concentrations were then isolated. Subcutaneous injection of parental SCCVII cells results in tumour development, while a mixture of IL-12-producing and non-producing cells results in tumour clearance. Interestingly, when comparing mice injected a mixture of SCCVII and either high IL-12-producing tumour cells or low IL-12-producing tumour cells, we observed that mixtures containing small amounts of high producing cells lead to tumour clearance, whereas mixtures containing large amounts of low producing cells fail to elicit protection, despite the production of equal amounts of total IL-12 in both mixtures. Furthermore, immunizing mice with IL-12-producing cells leads to the establishment of both local and systemic immunity against challenge with SCCVII. Using depletion antibodies, it was shown that both CD4+ and CD8+ cells are crucial for therapy. Lastly, we have established cell clones of other solid tumour cell lines (RM-1, LLC1 and moto1.1) that produce IL-12. Our results show that the delivery of IL-12 by cancer cells is an effective route for immune activation.

[836]

**TÍTULO / TITLE:** - Detecting Mechanisms of Acquired BRAF Inhibitor Resistance in Melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Methods Mol Biol. 2014;1102:163-74. doi: 10.1007/978-1-62703-727-3\_10.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-727-3\\_10](#)

**AUTORES / AUTHORS:** - Lo RS; Shi H

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California, Los Angeles, CA, USA.

**RESUMEN / SUMMARY:** - (V600)BRAF mutation was identified as an ideal target for clinical therapy due to its indispensable roles in supporting melanoma initiation and

progression. Despite the fact that BRAF inhibitors (BRAFi) can elicit anti-tumor responses in the majority of treated patients and confer overall survival benefits, acquired drug resistance is a formidable obstacle to long-term management of the disease. Several aberrant events including RTK upregulation, NRAS mutation, mutant BRAF amplification or alternative splicing, and MEK mutation have been reported as acquired BRAFi resistance mechanisms. Clinically, detection of these resistance mechanisms help understand drug response patterns and help guide combinatorial therapeutic strategies. Therefore, quick and accurate diagnosis of the resistant mechanisms in tumor biopsies has become an important starting point for personalized therapy. In this chapter, we review the major acquired BRAFi resistance mechanisms, highlight their therapeutic implications, and provide the diagnostic methods from clinical samples.

[837]

**TÍTULO / TITLE:** - GSK3 inhibitors regulate MYCN mRNA levels and reduce neuroblastoma cell viability through multiple mechanisms including p53 and Wnt signalling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 26.

- [Enlace al texto completo \(gratis o de pago\) 1158/1535-7163.MCT-13-0560-T](#)

**AUTORES / AUTHORS:** - Duffy DJ; Krstic A; Schwarzl T; Higgins DG; Kolch W

**INSTITUCIÓN / INSTITUTION:** - 1Systems Biology Ireland, University College Dublin.

**RESUMEN / SUMMARY:** - Neuroblastoma is an embryonal tumour accounting for approximately 15% of childhood cancer deaths. There exists a clinical need to identify novel therapeutic targets, particularly for treatment resistant forms of neuroblastoma. Therefore, we investigated the role the neuronal master regulator GSK3 in controlling neuroblastoma cell fate. We identified novel GSK3 mediated regulation of MYC (c-MYC and MYCN) mRNA levels, which may have implications for numerous MYC driven cancers. In addition, we showed that certain GSK3 inhibitors induced large scale cell death in neuroblastoma cells, primarily through activating apoptosis. mRNA-seq of GSK3 inhibitor treated cells was performed and subsequent pathway analysis revealed that multiple signalling pathways contributed to the loss of neuroblastoma cell viability. The contribution of two of the signalling pathways highlighted by the mRNA-seq analysis was functionally validated. Inhibition of the p53 tumour suppressor partly rescued the cell death phenotype, while activation of canonical Wnt signalling contributed to the loss of viability, in a p53 independent manner. Two GSK3 inhibitors (BIO-acetoxime and LiCl) and one small molecule Wnt agonist (Wnt Agonist 1) demonstrated therapeutic potential for neuroblastoma treatment. These inhibitors reduced the viability of numerous neuroblastoma cell lines, even those derived from high risk MYCN amplified metastatic tumours, for which effective therapeutics are currently lacking. Furthermore, while LiCl was lethal to neuroblastoma cells it did not reduce the viability of differentiated neurons. Taken together our data suggests that these small molecules may hold potential as effective therapeutic agents for the treatment of neuroblastoma and other MYC driven cancers.

[838]

**TÍTULO / TITLE:** - Dose-escalated salvage radiotherapy after radical prostatectomy in high risk prostate cancer patients without hormone therapy: outcome, prognostic factors and late toxicity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Radiat Oncol. 2013 Nov 27;8(1):276.

●● Enlace al texto completo (gratis o de pago) [1186/1748-717X-8-276](#)

**AUTORES / AUTHORS:** - Shelan M; Abo-Madyan Y; Welzel G; Bolenz C; Kosakowski J; Behnam N; Wenz F; Lohr F

**RESUMEN / SUMMARY:** - Purpose: Evaluation of dose escalated salvage radiotherapy (SRT) in patients after radical prostatectomy (RP) who had never received antihormonal therapy. To investigate prognostic factors of the outcome of SRT and to analyze which patient subsets benefit most from dose escalation. Materials and methods: Between 2002 and 2008, 76 patients were treated in three different dose-groups: an earlier cohort treated with 66 Gy irrespective of pre-RT-characteristics and two later cohorts treated with 70 Gy or 75 Gy depending on pre-RT-characteristics. Biochemical-relapse-free-survival (bRFS), clinical-relapse-free-survival (cRFS) and late toxicity were evaluated. RESULTS: Four-year bRFS and cRFS were 62.5% and 85%. Gleason score <8, positive surgical resection margin (PSRM) and low PSA (<=0.5 ng/ml) before SRT resulted in higher bRFS. Analysis of the whole group showed no clear dose-outcome relationship. Patients with PSRM, however, had improved bRFS when escalating >66 Gy. While > 70Gy did not improve the overall results, 4-year bRFS for patients with manifest local recurrence in the high-dose group was still comparable to those without manifest local recurrences. No grade 4 and minimal grade3 gastrointestinal and urinary toxicity were observed. CONCLUSIONS: Dose-escalated SRT achieves high biochemical control. The data strongly support the application of at least 70 Gy rather than 66 Gy. They do not prove positive effects of doses >70 Gy but do not disprove them as these doses were only applied to an unfavorable patients selection.

[839]

**TÍTULO / TITLE:** - A novel matrix metalloproteinase-2 inhibitor triazolylmethyl aziridine reduces melanoma cell invasion, angiogenesis and targets ERK1/2 phosphorylation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Enzyme Inhib Med Chem. 2013 Nov 19.

●● Enlace al texto completo (gratis o de pago) [3109/14756366.2013.855207](#)

**AUTORES / AUTHORS:** - Romanchikova N; Trapencieris P; Zemitis J; Turks M

**INSTITUCIÓN / INSTITUTION:** - Latvian Institute of Organic Synthesis , Riga , Latvia and.

**RESUMEN / SUMMARY:** - Abstract A novel matrix metalloproteinase-2 (MMP-2) inhibitor JaZ-30, which belongs to the class of C(2)-monosubstituted aziridine - aryl-1,2,3-triazole conjugates, was developed. MTT and crystal violet assays were used to determine cytotoxicity- IC(50) values of compound JaZ-30 on melanoma cell line B16 4A5. Our study proves the anti-cancer properties of JaZ-30 with a wide spectrum of activities. JaZ-30 was revealed as selective inhibitor of matrix metalloproteinase-2. JaZ-30-mediated decrease of Vascular Endothelial Growth Factor (VEGF) secretion results in inhibition of angiogenesis, performed with the human umbilical vein endothelial cell line (HUVEC-2) on Matrigel. A novel inhibitor decreases invasive

properties of melanoma cells measured in Matrigel chambers assay. JaZ-30 downregulates phosphorylation of the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in melanoma cells stimulated by phorbol-12-myristate-13-acetate (PMA). Our findings propose a novel MMP-2 inhibitor JaZ-30 as an attractive potential agent for melanoma treatment.

[840]

**TÍTULO / TITLE:** - ERCC1 expression does not predict survival and treatment response in advanced stage non-small cell lung cancer cases treated with platinum based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(8):4679-83.

**AUTORES / AUTHORS:** - Ozdemir O; Ozdemir P; Veral A; Uluer H; Ozhan MH

**INSTITUCIÓN / INSTITUTION:** - Department of Chest Diseases, Ege University Faculty of Medicine, Izmir, Turkey E-mail : [ozder\\_ozdemir@yahoo.com](mailto:ozder_ozdemir@yahoo.com).

**RESUMEN / SUMMARY:** - BACKGROUND: ERCC1 is considered as a promising molecular marker that may predict platinum based chemotherapy response in non small cell lung cancer patients. We therefore investigated whether its expression is indeed associated with clinical outcomes in advanced stage NSCLC patients. MATERIALS AND METHODS: Pretreatment tumor biopsy samples of 83 stage 3B and 4 non-small cell lung cancer patients treated with platinum based chemotherapy were retrospectively analyzed for immunohistochemical ERCC1 expression. None of the patients received curative surgery or radiotherapy. RESULTS: By calculating H- scores regarding the extent and intensity of immunohistochemical staining of tumor biopsy samples, ERCC1 expression was found to be positive in 50 patients (60.2%). ERCC1 positive and negative groups had no statistically significant differences regarding treatment response, progression free survival and overall survival (respectively  $p=0.161$ ;  $p=0.412$ ;  $p=0.823$ ). CONCLUSIONS: In our study we found no association between ERCC1 expression and survival or treatment response. The study has some limitations, such as small sample size and retrospective analysis method. There is need of more knowledge for use of ERCC1 guided chemotherapy regimens in advanced stage NSCLC.

[841]

**TÍTULO / TITLE:** - Safety and Tolerability of Tumor Necrosis Factor-alpha Inhibitors in Psoriasis: A Narrative Review.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Clin Dermatol. 2013 Nov 27.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s40257-013-0053-5](#)

**AUTORES / AUTHORS:** - Semble AL; Davis SA; Feldman SR

**INSTITUCIÓN / INSTITUTION:** - Center for Dermatology Research, Department of Dermatology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157-1071, USA.

**RESUMEN / SUMMARY:** - Tumor necrosis factor (TNF)-alpha inhibitors are an alternative to oral systemic therapies for psoriasis. Data regarding the safety of TNF-alpha inhibitors from randomized clinical trials may not fully reflect the effects on the

clinic patient population receiving the therapy, but other sources of information are available. We performed a literature review to assess the safety and tolerability of the treatment of moderate-to-severe plaque psoriasis with TNF-alpha inhibitors. A literature search was conducted using PubMed for articles dating from January 2000 to October 2013. Randomized controlled, cohort, open-label, and observational studies were included, as well as case reports and letters to the editor. Articles found on PubMed describing the safety of anti-TNF-alpha therapy in psoriasis patients were included, while studies highlighting interleukin (IL)-12 and IL-23 inhibitors were excluded, as were non-English articles. In total, 58 articles were included in the review. TNF-alpha inhibitors exhibit both efficacy and tolerability in patients with moderate-to-severe plaque psoriasis. Adverse effects associated with these medications are not common and can be minimized with routine clinical monitoring and patient education. While the risk of severe adverse events is low, the lack of very large, long-term, randomized safety trials limits the ability to fully define the safety of these agents. TNF-alpha inhibitors have a good efficacy/safety ratio for use in patients with moderate-to-severe psoriasis. Serious adverse effects are not common, and common injection-site reactions are usually manageable. The benefits of TNF-alpha inhibitors outweigh the risks for moderate-to-severe psoriasis; however, there are potential adverse effects and the patient populations at highest risk include the elderly and those with a history of malignancy.

[842]

**TÍTULO / TITLE:** - Doxorubicin in TAT peptide-modified multifunctional immunoliposomes demonstrates increased activity against both drug-sensitive and drug-resistant ovarian cancer models.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Biol Ther. 2013 Oct 21;15(1).

**AUTORES / AUTHORS:** - Apte A; Koren E; Koshkaryev A; Torchilin VP

**INSTITUCIÓN / INSTITUTION:** - Center for Pharmaceutical Biotechnology and Nanomedicine; Northeastern University; Boston, MA USA.

**RESUMEN / SUMMARY:** - Multidrug resistance (MDR) is a hallmark of cancer cells and a crucial factor in chemotherapy failure, cancer reappearance, and patient deterioration. We have previously described the physicochemical characteristics and the in vitro anticancer properties of a multifunctional doxorubicin-loaded liposomal formulation. Lipodox®, a commercially-available PEGylated liposomal doxorubicin, was made multifunctional by surface-decorating with a cell-penetrating peptide, TATp, conjugated to PEG 1000-PE, to enhance liposomal cell uptake. A pH-sensitive polymer, PEG 2000-Hz-PE, with a pH-sensitive hydrazone (Hz) bond to shield the peptide in the body and expose it only at the acidic tumor cell surface, was used as well. In addition, an anti-nucleosome monoclonal antibody 2C5 attached to a long-chain polymer to target nucleosomes overexpressed on the tumor cell surface was also present. Here, we report the in vitro cell uptake and cytotoxicity of the modified multifunctional immunoliposomes as well as the in vivo studies on tumor xenografts developed subcutaneously in nude mice with MDR and drug-sensitive human ovarian cancer cells (SKOV-3). Our results show the ability of multifunctional immunoliposomes to overcome MDR by enhancing cytotoxicity in drug-resistant cells, compared with non-modified liposomes. Furthermore, in comparison with the non-modified liposomes,

upon intravenous injection of these multifunctional immunoliposomes into mice with tumor xenografts, a significant reduction in tumor growth and enhanced therapeutic efficacy of the drug in both drug-resistant and drug-sensitive mice was obtained. The use of “smart” multifunctional delivery systems may provide the basis for an effective strategy to develop, improve, and overcome MDR cancers in the future.

[843]

**TÍTULO / TITLE:** - Anti-Apoptotic Pathways in Bone Marrow and Megakaryocytes in Myeloproliferative Neoplasia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pathobiology. 2013 Nov 20;81(2):60-68.

●● Enlace al texto completo (gratis o de pago) [1159/000356187](#)

**AUTORES / AUTHORS:** - Koopmans SM; Schouten HC; van Marion AM

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Maastricht University Medical Center, Maastricht, The Netherlands.

**RESUMEN / SUMMARY:** - Objective: Proliferative activity contributes to bone marrow cellularity in myeloproliferative neoplasia (MPN). Megakaryocytes are the most important cells in MPN bone marrow pathology. JAK2V617F mutation constitutively activates JAK2, pErk (phosphorylating extracellular signal-regulated kinase) and PI3K (phosphatidylinositol 3-kinase)-Akt signaling. Erk is involved in megakaryocyte differentiation, PI3K-Akt inhibits megakaryocyte apoptosis via Bcl-xL and two downstream effectors (p70S6k and Bnip3). Immunohistochemical expression of phosphorylated Erk, Akt, p70S6k and Bnip3 was studied along with microvessel density (MVD) in MPN bone marrow and megakaryocytes. Methods: 36 essential thrombocythemia (ET), 25 polycythemia vera and 45 primary myelofibrosis patients were analyzed for pErk, pAkt, Bnip3, p70S6k and MVD expression by immunostaining bone marrow biopsy sections followed by automated image analysis. JAK2V617F was analyzed through real-time PCR in blood samples. Results: pErk and pAkt were significantly higher expressed in MPN megakaryocytes, mainly in ET patients, compared to controls. Bnip3 was higher expressed in bone marrow of control patients and in MPN megakaryocytes. Mainly in ET patients, MPN megakaryocytes showed higher p70S6k expression compared to controls. Conclusion: Increased bone marrow cellularity in MPN patients might be influenced by increased pErk, pAkt and decreased Bnip3 expression. A dominant role for megakaryocytes in ET patients was shown. Increased amounts of megakaryocytes in MPN patients can be due to increased pAkt and p70S6k. © 2013 S. Karger AG, Basel.

[844]

**TÍTULO / TITLE:** - Conjunctival squamous cell carcinoma: paradoxical response to interferon eyedrops.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Arch Soc Esp Oftalmol. 2013 Apr 3. pii: S0365-6691(12)00554-0. doi: 10.1016/j.oftal.2012.12.010.

●● Enlace al texto completo (gratis o de pago) [1016/j.oftal.2012.12.010](#)

**AUTORES / AUTHORS:** - Mata E; Conesa E; Castro M; Martinez L; de Pablo C; Gonzalez ML

**INSTITUCIÓN / INSTITUTION:** - Servicio de Oftalmología, Hospital Central Cruz Roja San Jose y Santa Adela, Madrid, España.

**RESUMEN / SUMMARY:** - CASE REPORT: A 67 year-old male seen for a longstanding corneal-conjunctival tumor. Treatment: topical interferon alpha2b (IFN-alpha2b) 10 U/ml. A significant increase in lesion size was observed after 8 weeks. A surgical excision with cryotherapy was then performed. Pathological examination confirmed the diagnosis of squamous cell carcinoma. At this time the patient was found to have a positive HIV serology. DISCUSSION: Conjunctival intraepithelial neoplasia (CIN) is a pre-cancerous lesion of the ocular surface. Medical treatment of CIN is essentially with IFN-alpha2b due to its antiviral/antitumor properties. In patients with HIV, treatment response could be paradoxical. We recommend serology for HIV before treatment with topical IFN-alpha2b.

[845]

**TÍTULO / TITLE:** - Synergistic Combination of Novel Tubulin Inhibitor ABI-274 and Vemurafenib Overcome Vemurafenib Acquired Resistance in BRAFV600E Melanoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 Nov 18.

- Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0212](#)

**AUTORES / AUTHORS:** - Wang J; Chen J; Miller DD; Li W

**INSTITUCIÓN / INSTITUTION:** - 1Department of Pharmaceutical Sciences, University of Tennessee Health Science Center.

**RESUMEN / SUMMARY:** - Acquired clinical resistance to vemurafenib, a selective BRAFV600E inhibitor, arises frequently after short term chemotherapy. Since inhibitions of targets in the RAF-MEK-ERK pathway result in G0/G1 cell cycle arrest, vemurafenib-resistant cancer cells are expected to escape this cell cycle arrest and progress to subsequent G2/M phase. We hypothesized that a combined therapy using vemurafenib with a G2/M phase blocking agent will trap resistant cells and overcome vemurafenib resistance. To test this hypothesis, we first determined the combination index (CI) values of our novel tubulin inhibitor ABI-274 and vemurafenib on parental human A375 and MDA-MB-435 melanoma cell lines to be 0.32 and 0.1, respectively, suggesting strong synergy for the combination. We then developed an A375RF21 subline with significant acquired resistance to vemurafenib and confirmed the strong synergistic effect. Next we studied the potential mechanisms of overcoming vemurafenib resistance. Flow cytometry confirmed that the combination of ABI-274 and vemurafenib synergistically arrested cells in G1/G2/M phase, and significantly increased apoptosis in both parental A375 and the vemurafenib-resistant A375RF21 cells. Western blot analysis revealed that the combination treatment effectively reduced the level of phosphorylated and total AKT, activated the apoptosis cascade, and increased cleaved caspase-3 and cleaved PARP, but had no significant influence on the level of ERK phosphorylation. Finally, in vivo co-administration of vemurafenib with ABI-274 showed strong synergistic efficacy in the vemurafenib-resistant xenograft model in nude mice. Overall, these results offer a rational combination strategy to significantly enhance the therapeutic benefit in melanoma patients who inevitably become resistant to current vemurafenib therapy.

[846]

**TÍTULO / TITLE:** - Dilated papilla with mucin extrusion is a potential predictor of acute pancreatitis associated with intraductal papillary mucinous neoplasms of pancreas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pancreatology. 2013 Nov-Dec;13(6):615-20. doi: 10.1016/j.pan.2013.09.003. Epub 2013 Sep 30.

●● Enlace al texto completo (gratis o de pago) [1016/j.pan.2013.09.003](#)

**AUTORES / AUTHORS:** - Hata T; Sakata N; Okada T; Aoki T; Motoi F; Katayose Y; Egawa S; Unno M

**INSTITUCIÓN / INSTITUTION:** - Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND/OBJECTIVES: As intraductal papillary mucinous neoplasm (IPMN) of the pancreas is associated with acute pancreatitis (AP) in some cases, predicting the risk of pancreatitis is as important as predicting the risk of malignancy in IPMN cases. In this study, we attempted to clarify the characteristics of IPMN associated with AP, compared to those of IPMN not associated with AP. METHODS: From January 2006 to March 2013, data from 88 patients who underwent surgery for IPMN were retrospectively investigated and analyzed. We evaluated clinical and pathological variables of each patient and compared patients with IPMN with AP to those without AP. Furthermore, we presented representative cases of mild and severe pancreatitis caused by IPMN. RESULTS: Overall, 12 of 88 patients with IPMN (13.6%) had AP. Seven of the 12 patients had a single episode of AP, whereas the remaining 5 patients were diagnosed with IPMN with repeated AP. Ten of 12 patients with AP were diagnosed with mild AP and the remaining 2 with severe AP. Regarding clinical findings, the proportion of dilated papilla with mucin extrusion was significantly higher in patients with IPMN with AP than in those without AP ( $p = 0.035$ ). Histological findings indicated that the proportion of intestinal-subtype IPMN was significantly higher in patients with IPMN with AP ( $p = 0.013$ ). CONCLUSIONS: AP caused by IPMN derives mostly from intestinal IPMN. Dilated papilla with mucin extrusion can be a potential predictor of AP.

[847]

**TÍTULO / TITLE:** - Experimental validation of 5 in-silico predicted glioma biomarkers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neuro Oncol. 2013 Dec;15(12):1625-34. doi: 10.1093/neuonc/not124. Epub 2013 Oct 24.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not124](#)

**AUTORES / AUTHORS:** - Towner RA; Jensen RL; Vaillant B; Colman H; Saunders D; Giles CB; Wren JD

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**RESUMEN / SUMMARY:** - Background Glioblastoma multiforme (GBM) is a high-grade glioma with poor prognosis. Identification of new biomarkers specific to GBM could help in disease diagnosis. We have developed and validated a bioinformatics method to

predict proteins likely to be suitable as glioma biomarkers via a global microarray meta-analysis to identify uncharacterized genes consistently coexpressed with known glioma-associated genes. Methods A novel bioinformatics method was implemented called global microarray meta-analysis, using approximately 16 000 microarray experiments to identify uncharacterized genes consistently coexpressed with known glioma-associated genes. These novel biomarkers were validated as proteins highly expressed in human gliomas varying in tumor grades using immunohistochemistry. Glioma gene databases were used to assess delineation of expression of these markers in varying glioma grades and subtypes of GBM. Results We have identified 5 potential biomarkers-spondin1, Plexin-B2, SLIT3, fibulin-1, and LINGO1-that were validated as proteins highly expressed on the surface of human gliomas using immunohistochemistry. Expression of spondin1, Plexin-B2, and SLIT3 was significantly higher ( $P < .01$ ) in high-grade gliomas than in low-grade gliomas. These biomarkers were significant discriminators in grade IV gliomas compared with either grade III or II tumors and also distinguished between GBM subclasses. Conclusions This study strongly suggests that this type of bioinformatics approach has high translational potential to rapidly discern which poorly characterized proteins may be of clinical relevance.

[848]

**TÍTULO / TITLE:** - Beyond bevacizumab: investigating new angiogenesis inhibitors in ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Expert Opin Investig Drugs. 2013 Oct 11.

●● Enlace al texto completo (gratis o de pago) [1517/13543784.2013.839657](#)

**AUTORES / AUTHORS:** - Tomao F; Papa A; Rossi L; Caruso D; Zoratto F; Benedetti Panici P; Tomao S

**INSTITUCIÓN / INSTITUTION:** - 'Sapienza' University of Rome, Department of Gynaecology and Obstetrics, Policlinico 'Umberto I', Rome, Italy  
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**RESUMEN / SUMMARY:** - Introduction: Ovarian cancer is the most lethal gynecological cancer, mainly because of the advanced stage of the disease at diagnosis, with recent research investigating novel targets and agents into the clinical practice, with the aim to improve prognosis and quality of life. Angiogenesis is a significant target for ovarian cancer therapy. Areas covered: Areas covered in this review include the most common molecular pathways of angiogenesis, which have provided novel targets for tailored therapy in ovarian cancer patients. These therapeutic strategies comprise monoclonal antibodies and tyrosine kinase inhibitors. These drugs have as molecular targets such as vascular endothelial growth factor (VEGF), VEGF receptor, platelet-derived growth factor, fibroblast growth factor, angiopoietin and Ephrin type-A receptor 2. Expert opinion: The expansion in understanding the molecular biology that characterizes cancer cells has led to the rapid development of new agents to target important pathways, but the heterogeneity of ovarian cancer biology indicates that there is no predominant defect. This review attempts to discuss progress till date in tackling a more general target applicable to ovarian cancer angiogenesis.

[849]

**TÍTULO / TITLE:** - Effect of a Poly (ADP-Ribose) Polymerase-1 Inhibitor against Esophageal Squamous Cell Carcinoma Cell Lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Sci. 2013 Nov 13. doi: 10.1111/cas.12322.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12322](#)

**AUTORES / AUTHORS:** - Nasuno T; Mimaki S; Okamoto M; Esumi H; Tsuchihara K

**INSTITUCIÓN / INSTITUTION:** - Division of Translational Research, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan; Department of Otorhinolaryngology, University of Kitasato Hospital, 1-15-1 Kitasato, Minami-ku, Sagami-hara, Kanagawa, 252-0375, Japan.

**RESUMEN / SUMMARY:** - Effective molecular target drugs that improve therapeutic efficacy with fewer adverse effects for esophageal cancer are highly anticipated. Poly (ADP-ribose) polymerase (PARP) inhibitors have been proposed as low-toxicity agents to treat double strand break (DSB)-repair defective tumors. Several findings imply the potential relevance of DSB repair defects in the tumorigenesis of esophageal squamous cell carcinoma (ESCC). We evaluated the effect of a PARP Inhibitor (AZD2281) on the TE-series ESCC cell lines. Of these eight cell lines, the clonogenic survival of one (TE-6) was reduced by AZD2281 to the level of DSB repair-defective Capan-1 and HCC1937 cells. AZD2281-induced DNA damage was implied by increases in gamma-H2AX and cell cycle arrest at G2/M phase. The impairment of DSB repair in TE-6 cells was suggested by a sustained increase in gamma-H2AX levels and the tail moment calculated from a neutral comet assay after X-ray irradiation. Because the formation of nuclear DSB repair protein foci was impaired in TE-6 cells, whole-exome sequencing of these cells was performed to explore the gene mutations that might be responsible. A novel mutation in RNF8, an E3 ligase targeting gamma-H2AX was identified. Consistent with this, polyubiquitination of gamma-H2AX after irradiation was impaired in TE-6 cells. Thus, AZD2281 induced growth retardation of the DSB repair-impaired TE-6 cells. Interestingly, a strong correlation between basal expression levels of gamma-H2AX and sensitivity to AZD2281 was observed in the TE-series cells ( $R^2 = 0.5345$ ). Because the assessment of basal DSB status could serve as a biomarker for selecting PARP inhibitor-tractable tumors, further investigation is warranted. This article is protected by copyright. All rights reserved.

[850]

**TÍTULO / TITLE:** - Prognostic value of survivin and EGFR protein expression in triple-negative breast cancer (TNBC) patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Target Oncol. 2013 Nov 15.

●● Enlace al texto completo (gratis o de pago) [1007/s11523-013-0300-y](#)

**AUTORES / AUTHORS:** - Zhang M; Zhang X; Zhao S; Wang Y; Di W; Zhao G; Yang M; Zhang Q

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, The Third Affiliated Hospital of Harbin Medical University, Road 150 of Nangang District, Harbin, Heilongjiang Province, 150081, China.

**RESUMEN / SUMMARY:** - Triple-negative breast cancer (TNBC) is a particular type of breast cancer which is characterized by its biological aggressiveness, worse prognosis, and lack of prognostic markers or therapeutic targets in contrast with hormonal receptor-positive and human epidermal growth factor receptor 2-positive (HER2+) breast cancers. We aimed to evaluate survivin and epidermal growth factor receptor (EGFR) expression and their prognostic value and determine their relationships with the clinicopathological parameters of TNBC. A total of 136 patients who had undergone a resection of primary TNBC were enrolled at the Third Affiliated Hospital of Harbin Medical University from March 2003 to September 2005. Expression of ER, PR, HER2, EGFR, and survivin was assessed by immunohistochemistry. The association of TNBC and other clinicopathological variables and the prognostic value of survivin and EGFR expression were evaluated. Survivin was expressed in 62 (45.6 %) cases and EGFR was expressed in 82 (60.3 %) cases. Survivin expression was associated with menopausal status (P = 0.011), tumor size (P = 0.037), and lymph node status (P = 0.001). EGFR expression was associated with menopausal status (P = 0.029), lymph node status (P = 0.004), P53 expression (P = 0.001), Ki-67 expression (P = 0.028), and lymphatic vascular invasion (P = 0.037). A multivariate analysis demonstrated that tumor size (hazard ratio (HR) 1.587, 95 % confidence interval (CI) 1.081-2.330, P = 0.018 for disease-free survival (DFS); HR 1.606, 95%CI 1.096-2.354, P = 0.015 for overall survival (OS)), lymph node status (HR 2.873, 95%CI 1.544-5.344, P = 0.001 for DFS; HR 2.915, 95%CI 1.553-5.471, P = 0.001 for OS), tumor grade (HR 1.914, 95%CI 1.218-3.007, P = 0.005 for DFS; HR 1.983, 95%CI 1.228-3.203, P = 0.005 for OS), EGFR (HR 3.008, 95%CI 1.331-6.792, P = 0.008 for DFS; HR 3.151, 95%CI 1.374-7.226, P = 0.007 for OS), and survivin (HR 1.573, 95%CI 1.087-2.277, P = 0.016 for DFS; HR 1.607, 95%CI 1.088-2.374, P = 0.017 for OS) were of prognostic significance for disease-free and overall survival. We draw a conclusion from the present study that survivin and EGFR expression are useful prognostic markers of TNBC and might be useful for molecular targeting therapy of TNBC treatment.

[851]

**TÍTULO / TITLE:** - Polymorphisms in XPD Gene Could Predict Clinical Outcome of Platinum-Based Chemotherapy for Non-Small Cell Lung Cancer Patients: A Meta-Analysis of 24 Studies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 15;8(11):e79864. doi: 10.1371/journal.pone.0079864.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0079864](#)

**AUTORES / AUTHORS:** - Qin Q; Zhang C; Yang X; Zhu H; Yang B; Cai J; Cheng H; Ma J; Lu J; Zhan L; Liu J; Liu Z; Xu L; Sun X

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: Xeroderma pigmentosum group D (XPD) is an essential gene involved in the nucleotide excision repair (NER) pathway. Two commonly studied single nucleotide polymorphisms (SNPs) of XPD (Lys751Gln, A>C, rs13181; Asp312Asn, G>A, rs1799793) are implicated in the modulation of DNA repair capacity, thus related to the responses to platinum-based chemotherapy. Here we performed a meta-analysis to better evaluate the association between the two XPD SNPs and clinical outcome of platinum-based chemotherapy in non-small cell lung

cancer (NSCLC) patients. METHODS: A comprehensive search of PubMed database was conducted to identify relevant articles. Primary outcomes included objective response (i.e., complete response + partial response vs. stable disease + progressive disease), progression-free survival (PFS) and overall survival (OS). The pooled and 95% confidence intervals (CIs) of ORs (odds ratios) and HRs (hazard ratios) were estimated using the fixed or random effect model. RESULTS: Twenty-four studies were eligible according to the inclusion criteria. None of the XPD Lys751Gln/Asp312Asn polymorphisms was associated with objective response, PFS or OS in NSCLC patients treated with platinum drugs. However, in stratified analysis by ethnicity, the XPD Lys751Gln (A>C) polymorphism was not significantly associated with increased response in Caucasians (OR = 1.35, 95%CI = 1.0-1.83, P = 0.122 for heterogeneity) but was associated with decreased PFS in Asians (HR = 1.39, 95%CI = 1.07-1.81, P = 0.879 for heterogeneity). Furthermore, a statistically significant difference existed in the estimates of effect between the two ethnicities (P = 0.014 for TR; P<0.001 for PFS). CONCLUSIONS: XPD Lys751Gln (A>C) may have inverse predictive and prognostic role in platinum-based treatment of NSCLC according to different ethnicities. Further studies are needed to validate our findings.

[852]

**TÍTULO / TITLE:** - Prognostic significance of p53 immunoeexpression in the survival of oral squamous cell carcinoma patients treated with surgery and neoadjuvant chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Dec;6(6):1611-1615. Epub 2013 Oct 15.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ol.2013.1627](#)

**AUTORES / AUTHORS:** - Li L; Fukumoto M; Liu D

**INSTITUCIÓN / INSTITUTION:** - Guangdong Key Laboratory for Research and Development of Natural Drugs, Guangdong Medical College, Zhanjiang, Guangdong, P.R. China ; Department of Pathology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi, Japan.

**RESUMEN / SUMMARY:** - p53 status is a key biomarker for a variety of cancer types. However, it remains controversial whether p53 is an effective biomarker in oral squamous cell carcinoma (OSCC), particularly with regard to its prognostic value for OSCC patients with combinational treatment. The aim of the current study was to evaluate the prognostic potential of p53 immunoeexpression in samples from OSCC patients treated with surgery only or surgery and neoadjuvant chemotherapy. p53 expression was assessed immunohistochemically in biopsy tissues from 44 OSCC patients with a mean follow-up of 35.6 months. Correlations between p53 status, tumor size (T-classification), lymph node status (N-classification) and clinical outcome were analyzed. It was observed that p53-positive and N0 cases correlated with higher 5-year survival rates in cases treated with surgery alone (P=0.017 and P=0.03, respectively), while in cases with neoadjuvant chemotherapy, p53 status and lymph node status did not exhibit prognostic significance. Tumor size showed no prognostic value in cases receiving surgery alone or in those with neoadjuvant chemotherapy. The present results demonstrated for the first time that p53 immunohistochemical expression correlates with a good prognosis in OSCC patients receiving surgery alone. In conclusion, p53 immunohistochemical expression and lymph node status may

serve as prognostic markers for the survival of OSCC patients receiving surgery only, but not for patients undergoing surgery and neoadjuvant chemotherapy treatment.

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[853]

**TÍTULO / TITLE:** - Prognostic value of osteopontin in patients treated with primary radiotherapy for head and neck cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):5175-8.

**AUTORES / AUTHORS:** - Etiz D; Ataizi FC; Bayman E; Akcay M; Acikalin MF; Colak E; Ciftci E

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkey E-mail : [detiz@ogu.edu.tr](mailto:detiz@ogu.edu.tr).

**RESUMEN / SUMMARY:** - Background: The prognostic value of tumor osteopontin (OPN) in patients with squamous-cell head and neck cancer (SCHNC) was investigated. Materials and Methods: OPN expression was assessed by immunohistochemical methods in 50 patients, who were treated with primary radiotherapy (RT) for locally advanced SCHNC. The effects of OPN on clinical parameters, local-regional control after RT and metastasis-free survival, was assessed. Results: The rate of OPN expression in tumor tissue was 76%. OPN positive cases had lower Hb levels ( $p=0.088$ ). Mean time to local recurrence was 53.8 months (SE 3.9) in OPN-negative cases and 39.1 months (SE 4.7) in OPN-positive cases ( $p=0.047$ ). OPN increased the risk of local recurrence 5.9 times ( $p=0.085$ ). It had no effect on metastasis-free ( $p=0.116$ ) or overall survival ( $p=0.123$ ). OPN was positive in 12 of 19 cases that developed grade 3-4 acute radiation dermatitis ( $p=0.096$ ). Conclusions: OPN expression is associated with an increase in local recurrence in patients who were treated with primary RT for locally advanced SCHNC.

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[854]

**TÍTULO / TITLE:** - Plasma microRNAs predicting clinical outcome in metastatic colorectal cancer patients receiving first-line oxaliplatin-based treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Oncol. 2013 Sep 21. pii: S1574-7891(13)00125-7. doi: 10.1016/j.molonc.2013.09.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.molonc.2013.09.001](https://doi.org/10.1016/j.molonc.2013.09.001)

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**INSTITUCIÓN / INSTITUTION:** - Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Ullernchausen 70, 0310 Oslo, Norway.

**RESUMEN / SUMMARY:** - The conventional first-line chemotherapy for metastatic colorectal cancer (mCRC) consists of fluorouracil (5-FU) in combination with either oxaliplatin or irinotecan. We have explored microRNAs (miRNAs) in plasma as potential predictive markers to oxaliplatin-based chemotherapy. The expression of 742 miRNAs was examined in plasma samples from 24 mCRC patients (12 responders and 12 non-responders) before onset and after four cycles of 5-FU/oxaliplatin. The top differentially expressed miRNAs between responders and non-responders were selected for further analysis in a validation cohort of 150 patients. In the validation

cohort, there was a significant overrepresentation of miRNAs with higher mean expression in the non-responder group than in the responder group before treatment ( $p < 0.002$ ). Moreover, we found three miRNAs (miR-106a, miR-484, and miR-130b) to be significantly differentially expressed before treatment ( $p = 0.008$ ,  $0.008$ , and  $0.008$ , respectively). All three miRNAs were upregulated in non-responders. High expression of miR-27b, miR-148a, and miR-326 were associated with decreased progression-free survival (Hazard ratios (HR) of 1.4 (95% CI 1.1-1.8,  $p = 0.004$ ), 1.3 (95% CI 1.1-1.6,  $p = 0.007$ ), and 1.4 (95% CI 1.1-1.8,  $p = 0.008$ ), respectively). miR-326 was also associated with decreased overall survival (HR 1.5 (95% CI 1.1-2.0,  $p = 0.003$ )). There were no significantly differentially expressed miRNAs in association with clinical outcome after four cycles of chemotherapy. The present study demonstrates that plasma miRNAs analyzed before treatment may serve as non-invasive markers predicting outcome in mCRC patients treated with 5-FU and oxaliplatin-based chemotherapy.

[855]

**TÍTULO / TITLE:** - The forkhead transcription factor FOXO1 mediates cisplatin resistance in gastric cancer cells by activating phosphoinositide 3-kinase/Akt pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gastric Cancer. 2013 Nov 8.

●● Enlace al texto completo (gratis o de pago) [1007/s10120-013-0314-2](#)

**AUTORES / AUTHORS:** - Park J; Ko YS; Yoon J; Kim MA; Park JW; Kim WH; Choi Y; Kim JH; Cheon Y; Lee BL

**INSTITUCIÓN / INSTITUTION:** - Department of Tumor Biology, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Cisplatin (CDDP) is one of the most important chemotherapeutic agents in the treatment of advanced gastric cancer, but its efficacy is limited by CDDP resistance. Because the transcription factor FOXO1 is related to chemoresistance in various cancer cells, we investigated the function of FOXO1 in CDDP resistance in human gastric cancer cells. METHODS: Human gastric cancer cell lines MKN45 and SNU-601 were used. FOXO1 activation was modulated by transfection of FOXO1 AAA mutant gene or FOXO1 shRNA. The effects of FOXO1 on cell growth and CDDP cytotoxicity were assessed by crystal violet assay. Protein expressions of FOXO1, p110alpha, pAkt, and Akt were analyzed by Western blotting, and FOXO1 mRNA expression was evaluated by semiquantitative reverse transcription-polymerase chain reaction. FOXO1 activity was determined by luciferase reporter assay, and cell apoptosis was assessed by DAPI staining and Western blotting for PARP cleavage. RESULTS: Cisplatin treatment induced FOXO1 expression and activation in both gastric cancer cell lines. FOXO1 overexpression increased the CDDP resistance without changes in cell growth, whereas FOXO1 silencing enhanced CDDP cytotoxicity along with apoptotic characteristics. Both constitutive and CDDP-induced FOXO1 activations were accompanied by an increase in p110alpha and pAkt expression. Furthermore, Akt inhibition by LY294002 treatment restored the CDDP cytotoxicity that was suppressed by FOXO1 overexpression. CONCLUSION: FOXO1 inhibits CDDP-induced apoptosis in gastric cancer cells via activating PI3K/Akt pathway. Thus, FOXO1 may be a useful pharmacological indicator to predict CDDP efficacy in gastric cancer treatment.

[856]

**TÍTULO / TITLE:** - Prognostic significance of circulating tumor cells in advanced non-small cell lung cancer patients treated with docetaxel and gemcitabine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1128-8](#)

**AUTORES / AUTHORS:** - Juan O; Vidal J; Gisbert R; Munoz J; Macia S; Gomez-Codina J

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Department, Hospital Universitari I Politecnic La Fe, Bulevar Sur s/n, 46026, Valencia, España, [juan\\_osc@gva.es](mailto:juan_osc@gva.es).

**RESUMEN / SUMMARY:** - PURPOSE: To evaluate the association in the change of circulating tumor cell (CTC) levels and clinical outcomes (PFS and OS) in patients with advanced non-small cell lung cancer (NSCLC) treated homogeneously with docetaxel and gemcitabine administered every 2 weeks. METHODS: We prospectively evaluated 37 patients for CTC levels at baseline and after 2 months of chemotherapy (before third cycle). Detection was carried out with the CellSearch system. RESULTS: Nine of the 37 patients (24 %) had  $\geq 2$  CTCs at the baseline determination. Median progression-free survival (PFS) was 4.3 months (95 % CI 2.5-8.3) for patients with CTC 0-1 as compared to 9.4 months (95 % CI 1.2-12.2) for those with CTC  $\geq 2$  ( $p = 0.3506$ ). Median overall survival (OS) was 8.1 (95 % CI 2.8-16.3) and 12.2 (95 % CI 1.4-12.2) months for patients with 0-1 CTCs and  $\geq 2$  CTCs, respectively ( $p = 0.7639$ ). Patients with a second CTC quantification were classified as: group 1, CTC = 0-1 at baseline and CTC = 0-1 after second chemotherapy cycle (18 patients); group 2, CTC  $\geq 2$  at baseline and CTC = 0-1 after second determination (5 patients). Median PFS was 7.7 and 9.9 months for group 1 and group 2, respectively ( $p = 0.4467$ ). CONCLUSIONS: CTCs  $\geq 2$  at baseline were detected only in 24 % of this group of patients with advanced NSCLC and poor performance status. No significant differences in PFS and OS between patients with or without CTCs at baseline were observed.

[857]

**TÍTULO / TITLE:** - Patterns of Infection in Patients With Myelodysplastic Syndromes and Acute Myeloid Leukemia Receiving Azacitidine as Salvage Therapy. Implications for Primary Antifungal Prophylaxis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lymphoma Myeloma Leuk. 2013 Oct 1. pii: S2152-2650(13)00435-7. doi: 10.1016/j.clml.2013.09.014.

●● Enlace al texto completo (gratis o de pago) [1016/j.clml.2013.09.014](#)

**AUTORES / AUTHORS:** - Falantes JF; Calderon C; Marquez-Malaver FJ; Aguilar-Guisado M; Martin-Pena A; Martino ML; Montero I; Gonzalez J; Parody R; Perez-Simon JA; Espigado I

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS)/CSIC/Universidad de Sevilla, Sevilla, España. Electronic address: [josef.falantes.sspa@juntadeandalucia.es](mailto:josef.falantes.sspa@juntadeandalucia.es).

**RESUMEN / SUMMARY:** - Incidence, etiology, and outcome of infectious episodes in patients with myeloid neoplasms receiving azacitidine are uncertain, with no prospective data available in this group of patients. The aim of the current study was to analyze the incidence and factors related to the probability of infection in a cohort of

patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) treated with azacitidine who did not receive any type of antimicrobial prophylaxis. Significantly, the group of patients who received prior intensive chemotherapy had more infectious episodes ( $P = 10^{-4}$ ), and particularly, invasive aspergillosis ( $P = .015$ ), than patients who received frontline azacitidine. Primary antifungal prophylaxis might be recommended in MDS and AML patients receiving azacitidine as salvage therapy after intensive regimens.

[858]

**TÍTULO / TITLE:** - A Phase II Trial of Saracatinib, an Inhibitor of src Kinases, in Previously-Treated Advanced Non-Small-Cell Lung Cancer: The Princess Margaret Hospital Phase II Consortium.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lung Cancer. 2013 Oct 26. pii: S1525-7304(13)00178-2. doi: 10.1016/j.clcc.2013.08.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.clcc.2013.08.001](#)

**AUTORES / AUTHORS:** - Laurie SA; Goss GD; Shepherd FA; Neil Reaume M; Nicholas G; Philip L; Wang L; Schwock J; Hirsh V; Oza A; Tsao MS; Wright JJ; Leigh NB

**INSTITUCIÓN / INSTITUTION:** - The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, Ontario. Electronic address: [slaurie@toh.on.ca](mailto:slaurie@toh.on.ca).

**RESUMEN / SUMMARY:** - BACKGROUND: The src family of kinases may play a role in the malignant phenotype through effects on migration, motility, adhesion and proliferation. The activity of saracatinib, an orally available inhibitor of src kinases, was evaluated in patients with advanced, platinum-pretreated NSCLC. PATIENTS AND METHODS: Eligible patients with advanced NSCLC of any histologic subtype and who had obtained a best response to prior platinum-based chemotherapy of at least stable disease received saracatinib 175 mg orally daily in a 28 day cycle. The primary end point was the proportion of patients progression-free after 4 cycles (16 weeks) of therapy; 8 such patients of 32 evaluable were required to deem the therapy active. Immunohistochemistry for src expression was performed on archival tissue from enrolled patients. RESULTS: Thirty-seven patients received a median of 2 cycles (range, 1-14) each. Six of 31 evaluable patients were progression-free at 16 weeks. Two partial responses were observed, lasting 3.7 and 14.6 months; 1 responder had an EGFR exon 19 deletion. An additional 4 patients had stable disease for at least 4 cycles. The median progression-free and overall survival times were 1.8 and 7.6 months. No correlation between src protein expression and outcome was observed. CONCLUSIONS: There may be a subset of saracatinib-responsive NSCLC that is currently molecularly undefined. Further studies of this agent in a population preselected for target mutations that potentially relevant to src pathways, such as EGFR, should be considered.

[859]

**TÍTULO / TITLE:** - Prognostic significance of p21, p27 and survivin protein expression in patients with oral squamous cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Aug;6(2):381-386. Epub 2013 Jun 7.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1381](#)

**AUTORES / AUTHORS:** - Zhang M; Li J; Wang L; Tian Z; Zhang P; Xu Q; Zhang C; Wei F; Chen W

**INSTITUCIÓN / INSTITUTION:** - School Of Stomatology, Shandong University, Jinan, Shandong 250012; ; Department of Stomatology, Tai'an City Central Hospital, Tai'an, Shandong 271000;

**RESUMEN / SUMMARY:** - Oral squamous cell carcinoma (OSCC) accounts for >80% of head and neck malignancies. p21, p27 and survivin proteins are abnormally expressed in OSCC and have been previously reported to correlate with cell proliferation and apoptosis. However, the prognostic significance of p21, p27 and survivin remains controversial. The aim of the present study was to investigate the association of clinical parameters and prognosis with the levels of p21, p27 and survivin expression in patients with OSCC. The levels of the three biomarkers were evaluated by immunohistochemical staining in specimens from 110 patients with OSCC and each section was scored according to the percentage of positive tumor cells and staining intensity. Log-rank test and Cox proportional hazards regression were performed to assess the correlation between biomarkers and clinical events. The association between the immunoexpression of p21, p27 and survivin and clinical pathological variables were analyzed by the chi2 test and a non-parametric analysis. The expression of p21 in patients with OSCC was found to correlate with the expression of p27 and survivin. The results of the current study revealed that the five-year survival rate was significantly lower in patients with high p21 expression. In addition, the expression of p27 also showed a negative correlation with the five-year survival rate of OSCC, but to a lesser extent. By contrast, the expression of survivin was not a prognostic factor for OSCC. A Kaplan-Meier analysis and Cox proportional hazards model showed that lymph node metastasis and p21 expression were independent prognostic factors of OSCC.

[860]

**TÍTULO / TITLE:** - Prediction of response to pegylated interferon/ribavirin combination therapy for chronic hepatitis C genotypes 2a and 2b and high viral load.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dig Dis. 2013;31(5-6):426-33. doi: 10.1159/000355381. Epub 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1159/000355381](#)

**AUTORES / AUTHORS:** - Kim SR; El-Shamy A; Imoto S; Kim KI; Sugimoto K; Kim SK; Tanaka Y; Hatae T; Hasegawa Y; Fujinami A; Ohta M; Hotta H; Kudo M

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Kobe Asahi Hospital, Kobe, Japan.

**RESUMEN / SUMMARY:** - Objective: We investigated the impact of host genetics represented by the single nucleotide polymorphism (SNP) of the IL28B gene and viral genetic variations within the nonstructural protein 5A (NS5A) [including the interferon (IFN)/ribavirin (RBV) resistance-determining region (IRRDR) and the IFN sensitivity-determining region (ISDR)] on the outcome of pegylated IFN and RBV (PEG-IFN/RBV) treatment. Methods: Sixty-six patients infected with hepatitis C virus (HCV)-2a or HCV-2b who received PEG-IFN/RBV for 24 weeks were examined. Results: In HCV-2a, the major genotype of IL28B SNP showed a tendency toward association with sustained virological response (SVR) and rapid virological response (RVR), and four or more mutations in IRRDR (IRRDR[2a] >=4) and one or more mutations in ISDR plus its

carboxyl-flanking region (ISDR/+C[2a]  $\geq 1$ ) were significantly associated with SVR and RVR. In HCV-2b, one or more mutations in the N-terminal part of IRRDR (IRRDR/N[2b]  $\geq 1$ ) were significantly associated with RVR. Multivariate analysis identified the major genotype of IL28B SNP and IRRDR[2a]  $\geq 4$  as independent predictive factors of SVR in HCV-2a, with IRRDR[2a]  $\geq 4$  being more powerful than the IL28B SNP. Also, IRRDR[2a]  $\geq 4$  in HCV-2a and IRRDR/N[2b]  $\geq 1$  in HCV-2b were significant determiners of RVR. Conclusion: The NS5A sequence heterogeneity and IL28B SNP are useful factors to predict the sensitivity to PEG-IFN/RBV therapy in HCV-2a and HCV-2b infections. © 2013 S. Karger AG, Basel.

[861]

**TÍTULO / TITLE:** - Renal cell neoplasias: reversion-inducing cysteine-rich protein with Kazal motifs discriminates tumor subtypes, while extracellular matrix metalloproteinase inducer indicates prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 Oct 16;11(1):258.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1479-5876-11-258](#)

**AUTORES / AUTHORS:** - Rabien A; Stephan C; Kilic E; Weichert W; Kristiansen G; Miller K; Jung K; Erbersdobler A

**RESUMEN / SUMMARY:** - BACKGROUND: Matrix metalloproteinases can promote invasion and metastasis, which are very frequent in renal cell carcinoma even at the time of diagnosis. Knowing the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) as an inhibitor of matrix metalloproteinases and the extracellular matrix metalloproteinase inducer (EMMPRIN) protein as inducer, we aimed to determine their expression, localization and possible antagonistic action in the pathogenesis and progression of renal cell tumors in a retrospective study. METHODS: Tumor and adjacent normal tissues of 395 nephrectomized patients were immunostained for RECK and EMMPRIN on a tissue microarray. RESULTS: RECK strongly decreased in renal cell carcinoma compared to normal counterparts (Wilcoxon signed rank test,  $P < 0.001$ ), and it discriminated tumor entities showing the highest expression in oncocytomas. EMMPRIN, however, could be significantly correlated to pT stage and Fuhrman grading (Spearman's correlation coefficient  $r_s = 0.289$  and  $r_s = 0.382$ , respectively). Higher expression of EMMPRIN was associated with decreased overall survival in Kaplan-Meier analysis ( $P < 0.001$ ), and the EMMPRIN level could independently predict survival for cases without metastasis and involvement of lymph nodes. Decreased RECK expression was confirmed by Western blotting in tissue of eight normal/tumor matches of patients after radical nephrectomy, whereas the EMMPRIN pattern appeared to be heterogeneous. CONCLUSIONS: We propose RECK down regulation in renal cell carcinoma to be an early event that facilitates tumor formation and progression. EMMPRIN, however, as a prognostic tumor marker, increases only when aggressiveness is proceeding and could add an additional step to invasive properties of renal cell carcinoma.

[862]

**TÍTULO / TITLE:** - Safety of nanoparticle albumin-bound paclitaxel administered to breast cancer patients with clinical contraindications to paclitaxel or docetaxel: Four case reports.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Oct;6(4):881-884. Epub 2013 Jul 17.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1471](#)

**AUTORES / AUTHORS:** - Kimura K; Tanaka S; Iwamoto M; Fujioka H; Takahashi Y; Sato N; Terasawa R; Tominaga T; Ikari A; Uchiyama K

**INSTITUCIÓN / INSTITUTION:** - Section of Breast and Endocrine Surgery, Department of General and Gastroenterological Surgery, Osaka Medical College, Takatsuki, Osaka 569-8686, Japan.

**RESUMEN / SUMMARY:** - Taxanes, including paclitaxel (PTX) and docetaxel (DOC), are poorly soluble in water due to their hydrophobic properties and thus, require solvents. However, use of these solvents has been associated with toxic responses, including a hypersensitivity reaction (HSR). Nanoparticle albumin-bound paclitaxel (nab-PTX) is a novel formulation of PTX, which allows reconstitution of the agent with a saline solution instead of solvents and administration without premedication for HSRs. The current study reports the safe administration of nab-PTX to four breast cancer patients considered clinically to have contraindications to PTX or DOC. Two of the patients had previously experienced HSRs to PTX or DOC and the other two patients had contraindications to steroids as a premedication for HSRs, since one patient suffered from diabetes and the other was a carrier of the hepatitis B virus. All 4 patients were safely administered nab-PTX. In conclusion, administration of nab-PTX appears to be effective for patients that have previously experienced HSRs to other taxanes or in those with contraindications to steroids.

[863]

**TÍTULO / TITLE:** - Tumor histological subtyping determined by hormone receptors and HER2 status defines different pathological complete response and outcome to dose-dense neoadjuvant chemotherapy in breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1116-z](#)

**AUTORES / AUTHORS:** - Sanchez-Munoz A; Plata-Fernandez Y; Fernandez M; Jaen-Morago A; Fernandez-Navarro M; de la Torre-Cabrera C; Ramirez-Tortosa C; Pascual J; Alba E; Sanchez-Rovira P

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology Service, Hospital Universitario Virgen de la Victoria, Campus Teatinos s/n, 29010, Malaga, España, [asmoncomed@yahoo.es](mailto:asmoncomed@yahoo.es).

**RESUMEN / SUMMARY:** - PURPOSE: To assess the impact in pathological complete response (pCR) and outcome of two dose-dense neoadjuvant chemotherapy (DDNC) regimens among different histological subtypes determined by hormonal receptor (HR) and HER2 status in breast cancer patients. METHODS: A total of 127 breast cancer patients were treated with DDNC in two prospective studies. A: adriamycin 40 mg/m<sup>2</sup> on day (d) 1 plus paclitaxel 150 mg/m<sup>2</sup> and gemcitabine 2,000 mg/m<sup>2</sup> on d2 for six cycles (n = 54). B: epirubicin 90 mg/m<sup>2</sup>, cyclophosphamide 600 mg/m<sup>2</sup> on d1 for three cycles, followed by paclitaxel 150 mg/m<sup>2</sup> and gemcitabine 2,500 mg/m<sup>2</sup> on d1 +/- trastuzumab according to HER2 status (n = 73). Histological subtypes of breast cancer

were 49 % HR+/HER2-, 17.5 % HR+/HER2+, 13.5 % HR-/HER2+ and 20 % HR-/HER2-. RESULTS: pCR (absence of invasive cells in breast and lymph node) was achieved in 35 patients (28 %). The pCR rate was significantly different between histological subtypes: HR+/HER2- (9 %), HR+/HER2+ (23 %), HR-/HER2+ (50 %), HR-/HER2- (56 %) ( $p < 0.001$ ). The median follow-up was 81 months (r: 15-150 months). HR-/HER2- tumor subtype had a significantly worse DFS compared to HR+/HER2- ( $p = 0.02$ ), RH+/HER2+ ( $p = 0.04$ ) and HR-/HER2+ tumor subtypes ( $p = 0.02$ ). HR-/HER2- tumor subtype had a significantly shorter OS compared to HR+/HER2- ( $p = 0.007$ ), RH+/HER2+ ( $p = 0.05$ ), and HR-/HER2+ ( $p = 0.03$ ) tumor subtypes. However, no significant difference was observed in DFS and OS among HR-/HER2- tumors that achieved a pCR. CONCLUSIONS: HR-/HER2- and HR-/HER2+ subtypes had a high pCR rate to DDNC. HR-/HER2- tumors had a worse outcome compared to other tumor subtypes but no significant difference was observed among HR-/HER2- tumors that achieved a pCR.

[864]

**TÍTULO / TITLE:** - Efficacy of Combination Treatment of the Inhibitor of Phosphatidylinositol-3-Kinase/Protein Kinase B Pathway BEZ235 and the Inhibitor of Extracellular Regulated Protein Kinase/Mitogen-activated Protein Kinase Pathway U0126 in A Tumor Cell Model.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2013 Oct;35(5):530-4. doi: 10.3881/j.issn.1000-503X.2013.05.009.

●● Enlace al texto completo (gratis o de pago) [3881/j.issn.1000-](#)

[503X.2013.05.009](#)

**AUTORES / AUTHORS:** - Xin-Xin C; Shu Z; Yu-Zhuo S

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Institute of Basic Medical Sciences, CAMS and PUMC, Beijing 100005, China.

**RESUMEN / SUMMARY:** - Objective To study the inhibitory effect of the dual usage of BEZ235 and U0126, the inhibitor of phosphatidylinositol-3-kinase/protein kinase B pathway and extracellular regulated protein kinase/mitogen-activated protein kinase pathway, respectively, on cell proliferation. Methods Phosphatase and tensin homolog knockout mouse embryonic fibroblast (PTEN<sup>-/-</sup>MEF) cell lines were used as the cellular model for malignant tumors. BEZ235, the dual inhibitor of phosphatidylinositol-3-kinase and mammalian target of rapamycin, and U0126, the inhibitor of mitogen-activated protein kinase were used to treat the cells individually and in a combination manner. The inhibitory effects to cell proliferation were monitored by MTT. Results Both BEZ235 and U0126 suppressed PTEN knockout cell proliferation, and their half inhibitory concentrations were 6.257 nmol/L and 22.85 μmol/L, respectively. However, the combination treatment of the two drugs showed antagonistic rather than synergistic effect on cell proliferation. Conclusion BEZ235 and U0126 are not suitable for a combined target therapy regimen.

[865]

**TÍTULO / TITLE:** - Prognostic significance of miR-34a and its target proteins of FOXP1, p53, and BCL2 in gastric MALT lymphoma and DLBCL.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gastric Cancer. 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [1007/s10120-013-0313-3](http://1007/s10120-013-0313-3)

**AUTORES / AUTHORS:** - He M; Gao L; Zhang S; Tao L; Wang J; Yang J; Zhu M

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Changhai Hospital, The Second Military Medical University, 168 Changhai Rd., Shanghai, 200433, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL), which are the two most common types of gastric lymphomas, have different clinicopathological features and molecular characteristics with distinct clinical outcomes. Tumor suppressor miR-34a connects the p53 network with forkhead box protein 1 (FOXP1) and BCL2. Here, we investigated the prognostic value of these molecules in gastric MALT lymphoma and DLBCL for use in routine clinical practice. METHODS: Relative miR-34a expression was detected by quantitative reverse transcriptase-polymerase chain reaction in 20 cases of MALT lymphomas and 20 cases of DLBCLs. Tissue microarray, in situ hybridization, and immunohistochemistry analysis were used to examine the expression of miR-34a and its regulated genes, FOXP1, p53, and BCL2 proteins, in 64 patients with gastric MALT lymphoma and in 58 patients with DLBCL. Helicobacter pylori infection, overall survival (OS), and progression-free survival (PFS) were documented. RESULTS: The expression level of miR-34a was markedly decreased in MALT lymphomas and DLBCLs compared to normal gastric tissues and peripheral blood mononuclear cells. miR-34a was present in the cytoplasm and nucleus of lymphocytes. Its expression was significantly downregulated in MALT and DLBCL lymphoma tissues, as compared with normal lymphocytes. The expression level of miR-34a in DLBCL was lower than in MALT lymphoma. FOXP1 was found to be positive in 48 %, p53 in 20 %, and BCL2 in 68 % of MALT lymphoma cases. The corresponding positive rates of these markers in DLBCL were 64, 57, and 52 %, respectively. High expression of FOXP1, p53, and BCL2 was seen in stage III and IV of both types of lymphomas. FOXP1, p53, and BCL2 positivity was associated with poor OS with both lymphoma types but OS with DLBCL was significantly lower than with MALT lymphoma. CONCLUSIONS: Decreased miR-34a expression and increased FOXP1, p53, and BCL2 coexpression to predict a poor OS for MALT lymphoma and DLBCL patients could become very important prognostic markers in daily clinical work. Further investigation of these changes may be of prognostic significance in clinical practice.

[866]

**TÍTULO / TITLE:** - Survivin Messenger RNA Levels in Epstein-Barr Virus-Positive Patients With Leukemic Low-Grade B-Cell Lymphomas Expressing the Latent Membrane Protein 1: Evidence of Apoptotic Function?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lymphoma Myeloma Leuk. 2013 Oct 1. pii: S2152-2650(13)00423-0. doi: 10.1016/j.clml.2013.09.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.clml.2013.09.002](http://1016/j.clml.2013.09.002)

**AUTORES / AUTHORS:** - Diamantopoulos PT; Polonyfi K; Sofotasiou M; Mantzourani M; Galanopoulos A; Spanakis N; Papadopoulou V; Kalala F; Iliakis T; Zareifi DS; Kodandreopoulou E; Vassilakopoulos T; Angelopoulou M; Siakantaris M; Terpos E; Variami E; Kollia P; Vaiopoulos G; Pangalis G; Viniou NA

**INSTITUCIÓN / INSTITUTION:** - First Department of Internal Medicine, Hematology Unit, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece. Electronic address: [pandiamantopoulos@gmail.com](mailto:pandiamantopoulos@gmail.com).

**RESUMEN / SUMMARY:** - BACKGROUND: Epstein-Barr virus (EBV) is a ubiquitous pathogen that chronically infects B lymphocytes and is implicated in the pathogenesis of lymphoproliferative diseases. Latent membrane protein 1 (LMP1), the major oncoprotein of the virus, has been shown to inhibit apoptosis and trigger survivin expression in malignant cell lines. LMP1 expression has been detected in patients with chronic lymphocytic leukemia, but its properties have not been studied in patients with low-grade B-cell lymphomas. Recent data show that LMP1 can simultaneously induce and inhibit apoptosis in B cells. We detected LMP1 messenger RNA (mRNA) in patients with leukemic low-grade B-cell lymphoma and correlated the expression of the antiapoptotic molecule survivin to that of LMP1 in this group of patients. PATIENTS AND METHODS: Peripheral whole blood from 64 patients with low-grade B-cell lymphoma was tested by quantitative reverse transcriptase-polymerase chain reaction (PCR) for the presence of the BXL1-1 gene of EBV, and positive samples were tested by conventional PCR for LMP1 expression. Accordingly, survivin mRNA levels were measured by quantitative reverse transcriptase PCR in all samples and compared between LMP1-positive (LMP1+) and LMP1- patients. RESULTS: The BXL1-1 gene was detected in 27 of 64 patients (42%). LMP1 was expressed in 22 of 27 (81%) EBV+ patients. Survivin expression was found to be 6.36 times higher in LMP1- patients than in LMP1+ patients (P = .008). CONCLUSION: Our results imply that in patients with non-EBV-related leukemic low-grade B-cell lymphoma, LMP1 expression is possibly correlated to apoptosis, as indicated by the lower survivin mRNA levels in LMP1+ patients.

[867]

**TÍTULO / TITLE:** - TNF-alpha -857C>T Genotype is Predictive of Clinical Response after Treatment with Definitive 5-Fluorouracil/cisplatin-based Chemoradiotherapy in Japanese Patients with Esophageal Squamous Cell Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Int J Med Sci. 2013 Oct 15;10(12):1755-60. doi: 10.7150/ijms.6749.

●● Enlace al texto completo (gratis o de pago) [7150/ijms.6749](http://7150/ijms.6749)

**AUTORES / AUTHORS:** - Omatsu H; Kuwahara A; Yamamori M; Fujita M; Okuno T; Miki I; Tamura T; Nishiguchi K; Okamura N; Nakamura T; Azuma T; Hirano T; Ozawa K; Hirai M

**INSTITUCIÓN / INSTITUTION:** - 1. Department of Hospital Pharmacy, School of Medicine, Kobe University, Kobe 650-0017, Japan; ; 2. Department of Pharmacotherapy, Programs for Applied Biomedicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima 734-8553, Japan;

**RESUMEN / SUMMARY:** - Background: Genotypes of tumor necrosis factor alpha (TNF-alpha) and its surface receptors, TNFRSF1A and TNFRSF1B, have been examined in terms of the progression, metastasis, clinical efficacy, and prognosis of various cancers; however, little is known about their effects on clinical outcome in patients with esophageal squamous cell carcinoma (ESCC). In this study, TNF-alpha and TNFRSF1A genotypes were retrospectively evaluated in terms of predicting clinical response, long-term survival, and severe acute toxicities in 46 male Japanese ESCC

patients treated with definitive 5-fluorouracil (5-FU)/cisplatin (CDDP)-based chemoradiotherapy (CRT). Methods: A course consisted of the continuous infusion of 5-FU at 400 mg/m<sup>2</sup>/day for days 1-5 and 8-12, the infusion of CDDP at 40 mg/m<sup>2</sup>/day on days 1 and 8, and radiation at 2 Gy/day on days 1-5, 8-12, and 15-19, with a second course being repeated after a 2-week interval. The TNF-alpha -1031T>C (rs1799964), -863C>A (rs1800630), -857C>T (rs1799724), -308G>A (rs1800629), -238G>A (rs361525), TNFRSF1A -609G>T (rs4149570), and 36A>G (rs767455) genotypes were evaluated. Results: The TNF-alpha -857C>T genotype was found to be predictive of clinical response, i.e., complete response or not (P = 0.010, Fisher's exact test), but had no effect on long-term survival (CC(-857) vs. CT(-857) + TT(-857), P = 0.072, Fisher's exact test, P = 0.070, Log-rank test). Conclusions: The TNF-alpha -857C>T genotype was found to be predictive of clinical response and was more likely to predict long-term survival in Japanese ESCC patients receiving definitive 5-FU/CDDP-based CRT. Further clinical investigations with a larger number of patients or experiments in vitro should be performed to assess the predictive value of this genotype following CRT.

[868]

**TÍTULO / TITLE:** - The Blood Neutrophil-to-lymphocyte Ratio Predicts Survival in Patients with Advanced Hepatocellular Carcinoma Receiving Sorafenib.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):5527-31.

**AUTORES / AUTHORS:** - Zheng YB; Zhao W; Liu B; Lu LG; He X; Huang JW; Li Y; Hu BS

**INSTITUCIÓN / INSTITUTION:** - Department of Interventional Radiology, Cancer Center, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China E-mail : [luligong1969@163.com](mailto:luligong1969@163.com).

**RESUMEN / SUMMARY:** - Background and Aim: Increasing evidence correlates the presence of systemic inflammation with poor survival in patients with hepatocellular carcinoma (HCC). The aim of this study was to investigate the prognostic significance of the blood neutrophil-to-lymphocyte ratio (NLR) in patients with advanced HCC who received sorafenib monotherapy. Methods: A total of sixty-five patients with advanced HCC, not eligible for locoregional therapy, treated with sorafenib were enrolled. Potential prognostic factors such as age, gender, tumoral characteristics, performance status and NLR were analyzed. Results: Median OS and TTP for the entire cohort were 10.0 months (95%CI, 7.6-12.3 months) and 4.5 months (95% CI, 4.0-4.9 months). The mean NLR at baseline was 2.89. The median OS of patients with a high NLR (>4) was 6.5 months (95%CI, 5.2-7.7 months) compared with 12.5 months (95%CI, 9.9-15.0) for patients with a normal NLR (<=4) (P=0.01). Age <=65, NLR >4, extrahepatic metastases and vascular invasion were all predictors of poorer overall survival. Multivariate analysis showed that NLR > 4, vascular invasion and extrahepatic metastases were independent predictors of poorer overall survival. The median TTP of patients with a high NLR was 2.5 months (95%CI, 1.4-3.6 months) compared with 4.5 months (95%CI, 3.9-5.1 months) for patients with a normal NLR (P=0.012). Conclusions: High baseline NLR was associated with worse OS and TTP for patients with advanced HCC treated with sorafenib.

[869]

**TÍTULO / TITLE:** - U.s. Food and drug administration approves Paclitaxel protein-bound particles (abraxane®) in combination with gemcitabine as first-line treatment of patients with metastatic pancreatic cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - JOP. 2013 Nov 10;14(6):686-8. doi: 10.6092/1590-8577/2028.

**AUTORES / AUTHORS:** - Saif MW

**INSTITUCIÓN / INSTITUTION:** - Tufts University School of Medicine. Boston, MA, USA.  
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[870]

**TÍTULO / TITLE:** - A first-in-human, phase 1, dose-escalation study of dinaciclib, a novel cyclin-dependent kinase inhibitor, administered weekly in subjects with advanced malignancies.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Transl Med. 2013 Oct 16;11(1):259.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1479-5876-11-259](#)

**AUTORES / AUTHORS:** - Nemunaitis JJ; Small KA; Kirschmeier P; Zhang D; Zhu Y; Jou YM; Statkevich P; Yao SL; Bannerji R

**RESUMEN / SUMMARY:** - BACKGROUND: Dinaciclib, a small-molecule, cyclin-dependent kinase inhibitor, inhibits cell cycle progression and proliferation in various tumor cell lines in vitro. We conducted an open-label, dose-escalation study to determine the safety, tolerability, and bioactivity of dinaciclib in adults with advanced malignancies. METHODS: Dinaciclib was administered starting at a dose of 0.33 mg/m<sup>2</sup>, as a 2-hour intravenous infusion once weekly for 3 weeks (on days 1, 8, and 15 of a 28-day cycle), to determine the maximum administered dose (MAD), dose-limiting toxicities (DLTs), recommended phase 2 dose (RP2D), and safety and tolerability. Pharmacodynamics of dinaciclib were assessed using an ex vivo phytohemagglutinin lymphocyte stimulation assay and immunohistochemistry staining for retinoblastoma protein phosphorylation in skin biopsies. Evidence of antitumor activity was assessed by sequential computed tomography imaging after every 2 treatment cycles. RESULTS: Forty-eight subjects with solid tumors were treated. The MAD was found to be 14 mg/m<sup>2</sup> and the RP2D was determined to be 12 mg/m<sup>2</sup>; DLTs at the MAD included orthostatic hypotension and elevated uric acid. Forty-seven (98%) subjects reported adverse events (AEs) across all dose levels; the most common AEs were nausea, anemia, decreased appetite, and fatigue. Dinaciclib administered at the RP2D significantly inhibited lymphocyte proliferation, demonstrating a pharmacodynamic effect. Ten subjects treated at a variety of doses achieved prolonged stable disease for at least 4 treatment cycles. CONCLUSIONS: Dinaciclib administered every week for 3 weeks (on days 1, 8, and 15 of a 28-day cycle) was generally safe and well tolerated. Initial bioactivity and observed disease stabilization support further evaluation of dinaciclib as a treatment option for patients with advanced solid malignancies. Trial registration: ClinicalTrials.gov #NCT00871663.

[871]

**TÍTULO / TITLE:** - Total genomic alteration as measured by SNP-array-based molecular karyotyping is predictive of overall survival in a cohort of MDS or AML patients treated with azacitidine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood Cancer J. 2013 Nov 1;3:e155. doi: 10.1038/bcj.2013.52.

●● Enlace al texto completo (gratis o de pago) [1038/bcj.2013.52](#)

**AUTORES / AUTHORS:** - Cluzeau T; Moreilhon C; Mounier N; Karsenti JM; Gastaud L; Garnier G; Re D; Montagne N; Gutnecht J; Auburger P; Fuzibet JG; Cassuto JP; Raynaud S

**INSTITUCIÓN / INSTITUTION:** - 1] Centre hospitalier universitaire Nice, Nice, France [2] Centre Meditteraneen de medecine moleculaire, INSERM U1065, Nice, France.

**RESUMEN / SUMMARY:** - Metaphase cytogenetics (MC) has a major role in the risk stratification of patients with myelodysplastic syndromes (MDSs) and can affect the choice of therapies. Azacitidine (AZA) has changed the outcome of patients with MDS or acute myeloid leukemia (AML) unfit for intensive chemotherapy. Identification of patients without the benefit of AZA would allow AZA combination or other drugs in first-line treatments. New whole-genome scanning technologies such as single nucleotide polymorphism microarray (SNP-A)-based molecular karyotyping (MK) improve the risk stratification in MDS and AML. Maintenance of genomic integrity is less than three megabases (Mbs) total disruption of the genome correlated with better overall survival (OS) in patients with lower-risk MDS. In this SNP-A study, we aimed at defining a cutoff value for total genomic copy number (CN) alterations (TGA) influencing the median OS in a cohort of 51 higher-risk MDS/AML patients treated with AZA. We observed that the relative risk of worse OS increased >100 Mb of TGA, as detected by SNP-A-based MK (8 and 15 months respectively, P=0.02). Our data suggest that precise measurement of TGA could provide predictive information in poor and very poor revised International Prognostic Scoring system (IPSS-R) patients treated with AZA.

[872]

**TÍTULO / TITLE:** - Scoring of prognostic parameters in patients with unresectable advanced or recurrent colorectal cancer undergoing chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Yonago Acta Med. 2013 Sep;56(3):69-72. Epub 2013 Sep 11.

**AUTORES / AUTHORS:** - Ikeguchi M; Shimoda R; Yamamoto M; Maeta Y; Ashida K; Saito H

**INSTITUCIÓN / INSTITUTION:** - Division of Surgical Oncology, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8504, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND: Suitable chemotherapy is needed to prolong the survival of patients with unresectable advanced or recurrent colorectal cancer. We scored the periodical changes of several prognostic markers during chemotherapy in patients with this type of cancer to discern the effectiveness of chemotherapy. METHODS: Twenty consecutive patients with unresectable advanced or recurrent colorectal cancer were enrolled. All patients underwent combination chemotherapy with oxaliplatin or irinotecan plus 5-fluorouracil/leucovorin. Neutrophil/lymphocyte ratio (NLR), serum C-reactive protein (CRP), serum carcinoembryonic antigen (CEA) and serum albumin (ALB) were compared between the two periods (before chemotherapy and 3 months after it was started) in each patient. The scoring system was as follows: points are added when a patient shows a

decrease of NLR, CRP and CEA and an increase of ALB at 3 months after the start of chemotherapy with a possible final score of +4. On the other hand, points are reduced if a patient shows an elevation of NLR, CRP and CEA and a decrease of ALB at 3 months after the start of chemotherapy with a possible final score of -4. RESULTS: At 3 months after the start of first line chemotherapy, 13 patients showed positive scores but 7 patients showed zero or minus scores. According to our scoring system, we found the mean survival time (MST) of the 13 patients with plus scores was 34 months and this was significantly better than that of the 7 patients who showed zero or minus scores ( $P = 0.0008$ ). CONCLUSION: Our new scoring system is useful but when we find that first line chemotherapy is ineffective, we need to change it to second line chemotherapy as soon as possible. That may be the best treatment for patients with unresectable advanced or recurrent colorectal cancer.

[873]

**TÍTULO / TITLE:** - A discovery study of daunorubicin induced cardiotoxicity in a sample of acute myeloid leukemia patients prioritizes P450 oxidoreductase polymorphisms as a potential risk factor.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Front Genet. 2013 Nov 11;4:231.

●● [Enlace al texto completo \(gratis o de pago\) 3389/fgene.2013.00231](#)

**AUTORES / AUTHORS:** - Lubieniecka JM; Graham J; Heffner D; Mottus R; Reid R; Hogge D; Grigliatti TA; Riggs WK

**INSTITUCIÓN / INSTITUTION:** - Department of Zoology, Life Sciences Institute, University of British Columbia Vancouver, BC, Canada ; Department of Statistics and Actuarial Science, Simon Fraser University Burnaby, BC, Canada.

**RESUMEN / SUMMARY:** - Anthracyclines are very effective chemotherapeutic agents; however, their use is hampered by the treatment-induced cardiotoxicity. Genetic variants that help define patient's sensitivity to anthracyclines will greatly improve the design of optimal chemotherapeutic regimens. However, identification of such variants is hampered by the lack of analytical approaches that address the complex, multi-genic character of anthracycline induced cardiotoxicity (AIC). Here, using a multi-SNP based approach, we examined 60 genes coding for proteins involved in drug metabolism and efflux and identified the P450 oxidoreductase (POR) gene to be most strongly associated with daunorubicin induced cardiotoxicity in a population of acute myeloid leukemia (AML) patients (FDR adjusted p-value of 0.15). In this sample of cancer patients, variation in the POR gene is estimated to account for some 11.6% of the variability in the drop of left ventricular ejection fraction (LVEF) after daunorubicin treatment, compared to the estimated 13.2% accounted for by the cumulative dose and ethnicity. In post-hoc analysis, this association was driven by 3 SNPs-the rs2868177, rs13240755, and rs4732513-through their linear interaction with cumulative daunorubicin dose. The unadjusted odds ratios (ORs) and confidence intervals (CIs) for rs2868177 and rs13240755 were estimated to be 1.89 (95% CI: 0.7435-4.819;  $p = 0.1756$ ) and 3.18 (95% CI: 1.223-8.27;  $p = 0.01376$ ), respectively. Although the contribution of POR variants is expected to be overestimated due to the multiple testing performed in this small pilot study, given that cumulative anthracycline dose is virtually the only factor used clinically to predict the risk of cardiotoxicity, the contribution that

genetic analyses of POR can make to the assessment of this risk is worthy of follow up in future investigations.

[874]

**TÍTULO / TITLE:** - Clinical Outcome With Platinum-Based Chemotherapy in Patients With Advanced Nonsquamous EGFR Wild-Type Non-Small-Cell Lung Cancer Segregated According to KRAS Mutation Status.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lung Cancer. 2013 Oct 17. pii: S1525-7304(13)00179-4. doi: 10.1016/j.clc.2013.08.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.clc.2013.08.002](#)

**AUTORES / AUTHORS:** - Metro G; Chiari R; Bennati C; Cenci M; Ricciuti B; Puma F; Flacco A; Rebonato A; Giannarelli D; Ludovini V; Bellezza G; Ferolla P; Minotti V; Crino L

**INSTITUCIÓN / INSTITUTION:** - Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy. Electronic address: [giulio.metro@yahoo.com](mailto:giulio.metro@yahoo.com).

**RESUMEN / SUMMARY:** - BACKGROUND: We hypothesized that KRAS mutations function as a marker of poor sensitivity to first-line platinum-based chemotherapy in patients with advanced nonsquamous EGFR wild-type (WT) non-small-cell lung cancer (NSCLC). PATIENTS AND METHODS: Consecutive advanced nonsquamous EGFR WT NSCLCs treated at the Medical Oncology of Perugia with simultaneous assessment of KRAS mutation status were eligible. Anaplastic lymphoma kinase (ALK) gene status was known in roughly half of the patients who had KRAS WT. RESULTS: Two hundred four patients were included. Among them, the 77 individuals carrying a KRAS-mutant phenotype experienced a significantly inferior outcome in terms of response rate ( $P = .04$ ), disease control rate ( $P = .05$ ), and progression-free survival (PFS) ( $P = .05$ ) compared with the EGFR WT/KRAS WT population. The association between KRAS mutation and shorter PFS remained statistically significant at multivariate analysis (hazard ratio [HR], 1.45). In addition, patients with KRAS mutations reported a significantly shorter overall survival (OS) compared with patients with EGFR WT/KRAS WT/ALK negativity ( $n = 64$ ) ( $P = .02$ ). Among patients with KRAS mutations, those harboring a mutation at codon 13 ( $n = 12$ ) performed worse than those with a mutation at codon 12 ( $n = 62$ ) in terms of both PFS and OS ( $P = .09$  for both). CONCLUSION: KRAS mutation appears to negatively affect sensitivity to first-line platinum-based chemotherapy in patients with advanced nonsquamous EGFR WT NSCLC. Studies on larger case series are needed to address differences in clinical outcome according to the type of mutation.

[875]

**TÍTULO / TITLE:** - Hybrid method for prediction of metastasis in breast cancer patients using gene expression signals.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Signals Sens. 2013 Apr;3(2):79-86.

**AUTORES / AUTHORS:** - Dehnavi AM; Sehhati MR; Rabbani H

**INSTITUCIÓN / INSTITUTION:** - Department of Biomedical Engineering, Isfahan University of Medical Sciences, Isfahan, Iran.

**RESUMEN / SUMMARY:** - Using primary tumor gene expression has been shown to have the ability of finding metastasis-driving gene markers for prediction of breast cancer recurrence (BCR). However, there are some difficulties associated with analysis of microarray data, which led to poor predictive power and inconsistency of previously introduced gene signatures. In this study, a hybrid method was proposed for identifying more predictive gene signatures from microarray datasets. Initially, the parameters of a Rough-Set (RS) theory based feature selection method were tuned to construct a customized gene extraction algorithm. Afterward, using RS gene selection method the most informative genes selected from six independent breast cancer datasets. Then, combined set of these six signature sets, containing 114 genes, was evaluated for prediction of BCR. In final, a meta-signature, containing 18 genes, selected from the combination of datasets and its prediction accuracy compared to the combined signature. The results of 10-fold cross-validation test showed acceptable misclassification error rate (MCR) over 1338 cases of breast cancer patients. In comparison to a recent similar work, our approach reached more than 5% reduction in MCR using a fewer number of genes for prediction. The results also demonstrated 7% improvement in average accuracy in six utilized datasets, using the combined set of 114 genes in comparison with 18-genes meta-signature. In this study, a more informative gene signature was selected for prediction of BCR using a RS based gene extraction algorithm. To conclude, combining different signatures demonstrated more stable prediction over independent datasets.

[876]

**TÍTULO / TITLE:** - Low expression of mixed lineage kinase domain-like protein is associated with poor prognosis in ovarian cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Onco Targets Ther. 2013 Oct 30;6:1539-43. doi: 10.2147/OTT.S52805.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S52805](#)

**AUTORES / AUTHORS:** - He L; Peng K; Liu Y; Xiong J; Zhu FF

**INSTITUCIÓN / INSTITUTION:** - Department of Gynecology and Obstetrics, The Second Xiangya Hospital of Central South University, People's Republic of China.

**RESUMEN / SUMMARY:** - BACKGROUND: Mixed lineage kinase domain-like protein (MLKL) was initially identified as a key receptor interacting protein 3 downstream component of tumor-necrosis-factor-induced necrosis. In this study, we characterized the expression of MLKL in ovarian carcinomas and evaluated the prognostic value of MLKL in patients with ovarian cancer. MATERIALS AND METHODS: The ovarian cancer tissue specimens were collected from 153 patients diagnosed as primary ovarian cancer after operation at The Second Xiangya Hospital from January 2005 to December 2008. Immunohistochemistry was performed for MLKL and the protein expression score was quantified using an established scoring system. Kaplan-Meier survival curves were generated for disease-free survival (DFS) and overall survival (OS) for all patients. MLKL expression levels were correlated with DFS and OS using univariate and multivariate Cox regression analysis. RESULTS: Seventy-five patients (49%) were defined as having high MLKL expression and 67 patients (43.7%) had >80% of cells staining for MLKL. Remarkably, low MLKL expression was significantly associated with decreased DFS (median 40 months versus 25 months, P=0.0282) and OS (median 43 months versus 28 months, P=0.0032). In multivariate analysis, retained

significance was also observed. CONCLUSION: Low MLKL expression was significantly associated with both decreased DFS and OS in patients with primary ovarian cancer. MLKL expression may serve as a potential prognostic marker in patients with ovarian cancer.

[877]

**TÍTULO / TITLE:** - Clinical significance of ischemia-modified albumin in the diagnosis of Doxorubicin-induced myocardial injury in breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 4;8(11):e79426. doi: 10.1371/journal.pone.0079426.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0079426](http://1371/journal.pone.0079426)

**AUTORES / AUTHORS:** - Ma Y; Kang W; Bao Y; Jiao F; Ma Y

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer, The 463<sup>rd</sup> Hospital of the Chinese PLA, Shenyang, Liaoning, People's Republic of China.

**RESUMEN / SUMMARY:** - BACKGROUND: Ischemia-modified albumin is an altered serum albumin that forms under conditions of oxidative stress, a state also associated with doxorubicin-induced myocardial injury. OBJECTIVE: The aim of this study was to better assess diagnostic and prognostic significance of ischemia-modified albumin in patients with breast cancer undergoing doxorubicin chemotherapy. METHODS: Blood samples were collected from 152 breast cancer patients before and after each cycle of doxorubicin chemotherapy to measure the serum levels of ischemia-modified albumin, cardiac troponin T and creatine kinase-MB. We also monitored cardiac function during a 12 month follow-up. RESULTS: There was a significant difference in ischemia-modified albumin levels before and after each cycle of chemotherapy and the ischemia-modified albumin concentration positively correlated with the cumulative dose of doxorubicin ( $r = 0.212$ ,  $P < 0.05$ ). The combination of ischemia-modified albumin with cardiac troponin T and creatine kinase-MB increased the sensitivity to 0.920 and the specificity to 0.830 in the diagnosis of doxorubicin-induced myocardial injury. The optimal cutoff for ischemia-modified albumin concentration was 112.09 U/ml. The rate of change for ischemia-modified albumin levels correlated negatively with the rate of change for left ventricular ejection fraction at one year ( $r = -0.221$ ,  $P < 0.05$ ). CONCLUSION: Ischemia-modified albumin may be a clinically potential new marker for diagnosing doxorubicin-induced myocardial injury, and is helpful to predict long-term impairment of cardiac function.

[878]

**TÍTULO / TITLE:** - The predictive value of 53BP1 and BRCA1 mRNA expression in advanced non-small-cell lung cancer patients treated with first-line platinum-based chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncotarget. 2013 Oct;4(10):1572-81.

**AUTORES / AUTHORS:** - Bonanno L; Costa C; Majem M; Sanchez JJ; Gimenez-Capitan A; Rodriguez I; Vergnenegre A; Massuti B; Favaretto A; Rugge M; Pallares C; Taron M; Rosell R

**INSTITUCIÓN / INSTITUTION:** - Second Medical Oncology Unit, Istituto Oncologico Veneto I.R.C.C.S, Via Gattamelata 64, Padova, Italia.

**RESUMEN / SUMMARY:** - Platinum-based chemotherapy is the standard first-line treatment for non-oncogene- addicted non-small cell lung cancers (NSCLCs) and the analysis of multiple DNA repair genes could improve current models for predicting chemosensitivity. We investigated the potential predictive role of components of the 53BP1 pathway in conjunction with BRCA1. The mRNA expression of BRCA1, MDC1, CASPASE3, UBC13, RNF8, 53BP1, PIAS4, UBC9 and MMSET was analyzed by real-time PCR in 115 advanced NSCLC patients treated with first-line platinum-based chemotherapy. Patients expressing low levels of both BRCA1 and 53BP1 obtained a median progression-free survival of 10.3 months and overall survival of 19.3 months, while among those with low BRCA1 and high 53BP1 progression-free survival was 5.9 months (P less than 0.0001) and overall survival was 8.2 months (P=0.001). The expression of 53BP1 refines BRCA1-based predictive modeling to identify patients most likely to benefit from platinum-based chemotherapy.

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[879]

**TÍTULO / TITLE:** - Trends of clinical symptoms and prognosis of middle-aged prostate cancer patients after instigation of prostate specific antigen-based population screening.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Prostate Int. 2013;1(2):65-8. doi: 10.12954/PI.12017. Epub 2013 Jun 30.

●● Enlace al texto completo (gratis o de pago) [12954/PI.12017](#)

**AUTORES / AUTHORS:** - Kitagawa Y; Mizokami A; Namiki M

**INSTITUCIÓN / INSTITUTION:** - Department of Integrative Cancer Therapy and Urology, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan.

**RESUMEN / SUMMARY:** - **PURPOSE:** Due to the low rate of screening for prostate cancer in Japan, the incidence rates of cancer are high. We have established a prostate-specific antigen (PSA)-based screening system for prostate cancer in our region. We analyzed recent trends of clinical symptoms and prognosis of prostate cancer patients aged 55 to 69 years old in our institution. **METHODS:** Between 2000 and 2007, 162 cases of prostate cancer in patients aged 55 to 69 years old were newly diagnosed. The study population was divided into 119 cases with high PSA without symptoms, 36 cases with urological symptoms, and 7 cases with systemic symptoms. We analyzed the clinical courses of the patients in each group. **RESULTS:** The rate of localized disease was significantly higher in the PSA testing group than in the other groups. The median serum PSA levels were 1,600 ng/mL in the systemic symptom group, 13.3 ng/mL in the urological symptom group, and 7.1 ng/mL in the PSA testing group. The probability of nonrecurrence of the patients in the PSA testing group was significantly higher than in the other groups. **CONCLUSIONS:** The rate of prostate cancer patients diagnosed by PSA testing was relatively high in our institution. These patients have better prognosis than those with symptoms.

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[880]

**TÍTULO / TITLE:** - DNA Repair Capacity in Peripheral Blood Lymphocytes Predicts Efficacy of Platinum-based Chemotherapy in Patients with Gastric Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):5507-12.

**AUTORES / AUTHORS:** - Zhang YY; Gu KS

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine Oncology, the First Affiliated Hospital, Anhui Medical University, Hefei, China E-mail : [gks63@tom.com](mailto:gks63@tom.com).

**RESUMEN / SUMMARY:** - Objective: To investigate the correlation between ERCC1 expression levels in tumor tissue and peripheral blood lymphocytes (PBL) from patients with gastric cancer and assess the relationship between PBL DNA repair rate (DRR) and the efficacy of platinum chemotherapy. Methods: A total of 53 patients with gastric cancer receiving surgery and 20 controls were studied. ERCC1 protein expression in tumour tissue and PBL were determined by immunohistochemical staining. The PBL DRRs of 47 advanced patients and 20 controls were estimated by comet assay. Results: The positive expression rates of ERCC1 were 67.9%, 56.6% and 10.0% in tumour tissues, PBLs of gastric cancer patients, and PBLs of the control group. PBL ERCC1 expression correlated with that in tissue ( $\chi^2=15.463$ ,  $p=0.000$ ). Pearson contingency coefficient=0.475). DRRs of cancer patients by tail length (TL) ( $Z=4.662$ ,  $p=0.000$ ) and tail moment  $TM$  ( $Z=3.827$ ,  $p=0.000$ ) were significantly lower than that of control group. When TL was applied as an indicator, the correlation between DRR and chemotherapy efficacy was significant (Spearman rank correlation  $r=0.327$ ,  $p=0.032$ ). Patients with low levels of DRR in PBL presented better short-term efficacy of chemotherapy than those with high levels of DRR. Conclusions: The ERCC1 expression in PBLs may indirectly reflect ERCC1 expression in gastric cancer tissues. Compared with non-cancer populations, patients with gastric cancer may have lower DNA repair capacity. DRR in PBL may predict the short-term efficacy of platinum-based chemotherapy for patients with advanced gastric cancer.

[881]

**TÍTULO / TITLE:** - Differential Tumor Expression of Inhibitor of Differentiation-1 in Prostate Cancer Patients With Extreme Clinical Phenotypes and Prognostic Implications.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Genitourin Cancer. 2013 Oct 12. pii: S1558-7673(13)00210-3. doi: 10.1016/j.clgc.2013.08.007.

●● Enlace al texto completo (gratis o de pago) [1016/j.clgc.2013.08.007](http://1016/j.clgc.2013.08.007)

**AUTORES / AUTHORS:** - Ponz-Sarvise M; Castanon E; Panizo-Santos A; Redrado M; Lopez I; Rosell D; Gil-Aldea I; Calvo A; Nguewa PA; Gil-Bazo I

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Clinica Universidad de Navarra, Pamplona, España; Division of Oncology, Center for Applied Medical Research (CIMA), Pamplona, España.

**RESUMEN / SUMMARY:** - BACKGROUND: In the prostate-specific antigen era, potentially indolent prostate tumors are radically treated, causing overtreatment. Molecular prognostic factors might differentiate indolent from aggressive tumors, allowing avoidance of unnecessary treatment. PATIENTS AND METHODS: Fifty-two prostate cancer patients (20 organ-confined and 32 metastatic) were selected. All formalin-fixed and paraffin-embedded primary biopsies and matched metastases of 15 of them were evaluated for tumor and endothelial cell Id1 protein expression. Seventy-nine additional patients with organ-confined prostate cancer were selected for Id1 mRNA in silico analysis. RESULTS: Among metastatic cancer subjects, 48% of primary tumors and 38% of metastases showed Id1 tumor cell expression, and 79% of primary tumors and 81% of metastases showed endothelial immunoreactivity. In the organ-

confined group none of them showed Id1 protein tumor cell expression and 50% displayed endothelial expression. In the metastatic patients group, lower levels of Id1 protein predicted a nonsignificant longer overall survival (13 months vs. 7 months;  $P = .79$ ). In the in silico analysis, however, lower levels of Id1 mRNA predicted a longer disease-free survival (61 months vs. not-reached;  $P = .018$ ) and the hazard ratio for progression was 0.451 ( $P = .022$ ) in favor of patients showing lower levels.

**CONCLUSION:** In our cohort, it seems to be a differential epithelial expression of Id1 protein according to the prognostic features (metastatic/poor prognosis vs. organ-confined/good prognosis). In localized tumors treated with radical prostatectomy, higher Id1 mRNA expression levels might predict a higher hazard ratio for progression and a shorter disease-free survival. Further validation of these results in larger prospective series is warranted.

[882]

**TÍTULO / TITLE:** - Plasma levels of tissue inhibitor of matrix metalloproteinase-1 correlate with diagnosis and prognosis of glioma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin Med J (Engl). 2013 Nov;126(22):4295-300.

**AUTORES / AUTHORS:** - Lin Y; Wang JF; Gao GZ; Zhang GZ; Wang FL; Wang YJ

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, First Hospital of China Medical University, Shenyang, Liaoning 110001, China.

**RESUMEN / SUMMARY:** - **BACKGROUND:** There is no validated blood biomarker available for glioma management. Invasive growth is the key feature of glioma. We assessed the clinical usefulness of plasma tissue inhibitor of metalloproteinase 1 (TIMP-1), which has less molecular weight than metalloproteinases, as a potential blood biomarker for glioma. **METHODS:** A total of 285 patients and 59 normal subjects were studied. Plasma concentration of TIMP-1 was measured with enzyme-linked immunosorbent assay. Plasma TIMP-1 was compared between normal and glioma patients, between patients with different pathological grades, and between patients with different prognoses. Longitudinal changes in plasma TIMP-1 during treatment were also evaluated. Plasma matrix metalloproteinase (MMP)-9 level was also assayed and its clinical usefulness was compared with that of TIMP-1. **RESULTS:** Plasma TIMP-1 and MMP-9 were both increased in glioma patients compared with normal controls (TIMP-1:  $P < 0.001$ ; MMP-9:  $P = 0.007$ ). Plasma TIMP-1 increases with increased tumor grade. In Grade IV gliomas, plasma TIMP-1 significantly increased after "successful removal" of the tumor (paired samples t-test, before operation vs. during chemotherapy without recurrence,  $t = -2.131$ ,  $P = 0.038$ ), but did not change significantly at the time of tumor recurrence (during chemotherapy without recurrence vs. after tumor recurrence,  $t = -0.652$ ,  $P = 0.632$ ). High plasma TIMP-1 level correlated with better survival in Grade IV glioma patients (hazard ratio: 0.550, 95% CI: 0.101-1.000,  $P = 0.036$ ). In Grade IV gliomas, patients with higher plasma TIMP-1 had significantly longer survival time than those with lower plasma TIMP-1 level (25.23 vs. 18.95 months, log-rank  $P = 0.045$ ). Plasma MMP-9 did not show significant association with either the pathological grade or the prognosis of glioma patients. **CONCLUSIONS:** Plasma TIMP-1 is associated with the diagnosis and prognosis of glioma patients. It appears to have better usefulness for guiding clinical decision making than plasma MMP-9. Further studies in an expanded patient population are needed to better define its clinical usefulness.

[883]

**TÍTULO / TITLE:** - Role of cyclins A and E in endometrial carcinogenesis in breast cancer patients under tamoxifen treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Egypt Natl Canc Inst. 2013 Dec;25(4):193-8. doi: 10.1016/j.jnci.2013.07.002. Epub 2013 Jul 25.

●● Enlace al texto completo (gratis o de pago) [1016/j.jnci.2013.07.002](#)

**AUTORES / AUTHORS:** - Metwally AM; Refaat LA; Shaaban H; Megm S; Emara M; Tohamy AA; Sinna EA; Khaled H

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**RESUMEN / SUMMARY:** - PURPOSE: The objective of our study was to determine the relevance of cyclins A and E overexpression in endometrial carcinogenesis in hormone receptor-positive breast cancer patients under tamoxifen therapy. EXPERIMENTAL DESIGN: We assessed expression of cyclins A and E in Endometrial cytology samples collected from 36 ER and PR positive breast cancer patients; under tamoxifen treatment by using the Tao-brush non-invasive brushing cytology technique. Cyclins were detected in the collected samples by means of immuno-cytochemistry. The patients included in this study are a cohort of 36 breast cancer patients who were operated upon at the National Cancer Institute - Cairo University in the period from February 2006 to May 2008 and received tamoxifen (TAM) as part of their adjuvant treatment. RESULTS: Cyclins A and E were expressed in 17 and 15 of the 36 collected endometrial cytology samples (47.2% and 41.6% respectively). Expression of cyclins A and E was highly correlated to Tamoxifen exposure duration (32 and 43 months respectively)  $p < 0.001$ . Tamoxifen median exposure duration was shortened to 21 months in cases showing positivity for either markers, while in cases showing positivity for both cyclins, the median exposure duration was longer (44.5 months) ( $p < 0.001$ ). Neither cyclin A nor E was detected before median tamoxifen exposure duration of 11 months. Endometrial carcinoma cases had the longest Tamoxifen exposure duration (60 months). CONCLUSION: Cyclins A and E expression is involved in the carcinogenesis of endometrium in women with breast cancer and under tamoxifen-treatment. Follow up of the patients using these 2 markers is highly recommended starting from the 12<sup>th</sup> month.

[884]

**TÍTULO / TITLE:** - Hematopoietic growth factors support in the elderly cancer patients treated with antineoplastic chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Anticancer Agents Med Chem. 2013 Nov;13(9):1438-43.

**AUTORES / AUTHORS:** - Rupolo M; Lleshi A; Cacopardo B; Michieli M; Berretta M

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, National Cancer Institute of Aviano, Via Franco Gallini 2, 33081 Aviano (PN), Italy. [mrupolo@cro.it](mailto:mrupolo@cro.it).

**RESUMEN / SUMMARY:** - The 60% of tumors affected patients >65 years of age and the future projections are considering an amount of 70% after 2030. Elderly Patients presents multiple comorbidity, polypharmacy, and disability. Geriatric assessment helps

physicians to take the best therapeutic decisions. Clinical conditions influence efficacy and tolerability of chemotherapy. Prophylactic use of G-CSF after chemotherapy lowers the rate and length of severe neutropenia, and decreases the episodes of febrile neutropenia. Anemia is a hematologic condition associated with ageing, but is frequently associated to concomitant chronic disease. Stem cells display increasing resistance to erythropoietin in the elderly patients and this is connected with the onset of pro-inflammatory cytokines characteristic of this age. Anemia is a common adverse event in cancer patients receiving chemotherapy. Several of the symptoms associated with anemia, such as fatigue, syncope, palpitations and dyspnea, reduce patient activity and have a profound effect on the quality of life [QOL]. Considering the unfit or frail status of elderly patient the at home use of peg-filgrastim and weekly or three weekly erythropoietin administration could be preferred for this setting of patients that lack of specialized nursing care or facilities. Further studies, considering the several differences in health organizations in vary countries, could be held to state the real impact of the biosimilars in comparison to the long acting originators in the reduction of costs in this group of patients.

[885]

**TÍTULO / TITLE:** - Prognostic implication of serum vascular endothelial growth factor in advanced hepatocellular carcinoma staging.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Ann Hepatol. 2013 Nov-Dec;12(6):915-25.

**AUTORES / AUTHORS:** - Yegin EG; Siykhymbayev A; Eren F; Bekiroglu N; Ozdogan OC

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Marmara University, Faculty of Medicine, Istanbul, Turkey.

**RESUMEN / SUMMARY:** - BACKGROUND: Staging systems have considerable impact on hepatocellular carcinoma (HCC) treatment approaches and outcomes. There is an unmet need to improve their stratification ability. We have evaluated four commonly used staging systems and assessed whether angiogenic biomarker vascular endothelial growth factor (VEGF) could improve their prognostic stratification. MATERIAL AND METHODS: Four staging systems; Okuda, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer (BCLC), and Child-Pugh were evaluated in 78 HCC patients; their stratification abilities were detected by Kaplan-Meier curves and log-rank test; their accuracies of predicting survival were compared with the concordance index. Serum VEGF levels were measured using ELISA method. Recursive partitioning was used to determine the optimal VEGF cutoff. The prognostic significance of VEGF cutoff and other parameters were analyzed using univariate and multivariate models. RESULTS: None of the staging systems demonstrated better discriminatory ability in predicting survival. The four staging systems did not reveal significant differences in probability of survival across their intermediate-advanced stages. Optimal cutoff identified for VEGF was 445 pg/mL. In advanced HCC, VEGF level ( $p = 0.004$ ) and in early HCC, bilirubin level ( $p = 0.009$ ) were identified as the independent prognostic factors. Survival comparison with high and low VEGF levels was significant for advanced HCC, while insignificant for early disease. CONCLUSION: Staging systems with conventional parameters did not provide good prognostic stratification for survival in advanced HCC population. Serum VEGF level was an

independent predictor of survival in advanced HCC, and provided more survival homogeneity within the advanced stages of conventional staging systems.

[886]

**TÍTULO / TITLE:** - Can K-ras Gene Mutation Be Utilized as Prognostic Biomarker for Colorectal Cancer Patients Receiving Chemotherapy? A Meta-Analysis and Systematic Review.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 21;8(10):e77901. doi: 10.1371/journal.pone.0077901.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0077901](#)

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**INSTITUCIÓN / INSTITUTION:** - Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China ; Institute of Digestive Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

**RESUMEN / SUMMARY:** - INTRODUCTION: K-ras gene mutations were common in colorectal patients, but their relationship with prognosis was unclear. OBJECTIVE: Verify prognostic differences between patient with and without mutant K-ras genes by reviewing the published evidence. METHOD: Systematic reviews and data bases were searched for cohort/case-control studies of prognosis of colorectal cancer patients with detected K-ras mutations versus those without mutant K-ras genes, both of whom received chemotherapy. Number of patients, regimens of chemotherapy, and short-term or long-term survival rate (disease-free or overall) were extracted. Quality of studies was also evaluated. PRINCIPAL FINDINGS: 7 studies of comparisons with a control group were identified. No association between K-ras gene status with neither short-term disease free-survival (OR=1.01, 95% CI, 0.73-1.38, P=0.97) nor overall survival (OR=1.06, 95% CI, 0.82-1.36, P=0.66) in CRC patients who received chemotherapy was indicated. Comparison of long-term survival between two groups also indicated no significant difference after heterogeneity was eliminated (OR=1.09, 95% CI, 0.85-1.40, P=0.49). CONCLUSIONS: K-ras gene mutations may not be a prognostic index for colorectal cancer patients who received chemotherapy.

[887]

**TÍTULO / TITLE:** - Plasminogen Activator Inhibitor Type 1 ( ) A15T Gene Polymorphism Is Associated with Prognosis in Patients with Mutation Positive Pulmonary Adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Tuberc Respir Dis (Seoul). 2013 Oct;75(4):140-149. Epub 2013 Oct 29.

●● Enlace al texto completo (gratis o de pago) [4046/trd.2013.75.4.140](#)

**AUTORES / AUTHORS:** - Lim JE; Park MS; Kim EY; Jung JY; Kang YA; Kim YS; Kim SK; Shim HS; Cho BC; Chang J

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Hongik Hospital, Seoul, Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Plasminogen activator inhibitor type 1 (PAI-1), an important regulator of plasminogen activator system which controls degradation

of extracellular membrane and progression of tumor cells, and PAI-1 gene polymorphic variants have been known as the prognostic biomarkers of non-small cell lung cancer patients. Recently, experimental in vitro study revealed that transforming growth factor-beta1 initiated PAI-1 transcription through epithelial growth factor receptor (EGFR) signaling pathway. However, there is little clinical evidence on the association between PAI-1 A15T gene polymorphism and prognosis of Korean population with pulmonary adenocarcinoma and the influence of activating mutation of EGFR kinase domain. METHODS: We retrospectively reviewed the medical records of 171 patients who were diagnosed with pulmonary adenocarcinoma and undergone EGFR mutation analysis from 1995 through 2009. RESULTS: In all patients with pulmonary adenocarcinoma, there was no significant association between PAI-1 A15T polymorphic variants and prognosis for overall survival. However, further subgroup analysis showed that the group with AG/AA genotype had a shorter 3-year survival time than the group with GG genotype in patients with EGFR mutant-type pulmonary adenocarcinoma (mean survival time, 24.9 months vs. 32.5 months, respectively;  $p=0.015$ ). In multivariate analysis of 3-year survival for patients with pulmonary adenocarcinoma harboring mutant-type EGFR, the AG/AA genotype carriers had poorer prognosis than the GG genotype carriers (hazard ratio, 7.729; 95% confidence interval, 1.414-42.250;  $p=0.018$ ). CONCLUSION: According to our study of Korean population with pulmonary adenocarcinoma, AG/AA genotype of PAI-1 A15T would be a significant predictor of poor short-term survival in patients with pulmonary adenocarcinoma harboring mutant-type EGFR.

[888]

**TÍTULO / TITLE:** - LUNX mRNA-positive cells at different time points predict prognosis in patients with surgically resected nonsmall cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Transl Res. 2013 Oct 10. pii: S1931-5244(13)00303-4. doi: 10.1016/j.trsl.2013.09.010.

●● Enlace al texto completo (gratis o de pago) [1016/j.trsl.2013.09.010](#)

**AUTORES / AUTHORS:** - Li J; Shi SB; Shi WL; Wang Y; Yu LC; Zhu LR; Ge LP

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**RESUMEN / SUMMARY:** - LUNX is a lung-specific gene whose messenger ribonucleic acid (mRNA) expression is strictly limited to normal lung tissue and nonsmall cell lung cancer (NSCLC) tissue. The aim of this study was to investigate whether the detection of LUNX mRNA-positive circulating tumor cells (CTC)s in peripheral blood at different time points is useful for predicting disease recurrence, disease-free survival (DFS), and overall survival (OS) in NSCLC patients undergoing surgery. Serial blood samples from 68 patients with stage I-IIIa NSCLC were examined by real-time quantitative polymerase chain reaction assay targeting LUNX mRNA before (T0) and after surgery (T1) and after the completion of adjuvant chemotherapy (T2). Results showed that LUNX mRNA-positive CTCs were detected in 40 of 68 NSCLC patients (58.8%) before surgery; the detection rates of LUNX mRNA-positive CTCs at T1 and T2 time points were 32.4% (22/68) and 33.3% (20/60), respectively. The detection of LUNX mRNA-positive CTC at 3 time points was associated with lymph node status and pathologic stage. During the follow-up period, patients with LUNX mRNA-positive CTC at 3 time

points had a higher relapse rate and a shorter DFS and OS than those without. Multivariate analysis revealed that presence of LUNX mRNA-positive CTC at T1 and T2 time points was an independent unfavorable factor for DFS and OS. In conclusion, detection of LUNX mRNA-positive CTC after surgery and the completion of adjuvant chemotherapy in patients with stage I-IIIa NSCLC are highly predictive for DFS and OS. This technique could aid in the prediction of prognosis and design of tailored treatment.

[889]

**TÍTULO / TITLE:** - Posttreatment cut-off levels of squamous cell carcinoma antigen as a prognostic factor in patients with locally advanced cervical cancer treated with radiotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Gynecol Oncol. 2013 Oct;24(4):313-20. doi: 10.3802/jgo.2013.24.4.313. Epub 2013 Oct 2.

●● Enlace al texto completo (gratis o de pago) [3802/jgo.2013.24.4.313](#)

**AUTORES / AUTHORS:** - Kawaguchi R; Furukawa N; Kobayashi H; Asakawa I

**INSTITUCIÓN / INSTITUTION:** - Department of Obstetrics and Gynecology, Nara Medical University, Nara, Japan.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** The aim of the present study was to assess prognostic factors for patients with locally advanced cervical cancer treated with radiotherapy as the primary treatment and to assess the posttreatment cut-off levels of squamous cell carcinoma antigen (SCC-Ag) to predict three-year overall survival (OS) rates. **METHODS:** One hundred and twenty-eight patients with cervical squamous cell carcinoma (International Federation of Gynecology and Obstetrics [FIGO] stage IIB-IVA) treated using radiotherapy or concurrent chemoradiotherapy were identified. Of these patients, 116 who had SCC-Ag levels >1.5 ng/mL prior to treatment were analyzed retrospectively. **RESULTS:** Median age was 68 years (range, 27 to 79 years). The complete response rate was 70.7% and the three-year OS rate was 61.1%. The median levels of pretreatment and posttreatment SCC-Ag were 11.5 ng/mL (range, 1.6 to 310.0 ng/mL) and 0.9 ng/mL (range, 0.4 to 41.0 ng/mL), respectively. Multivariate analysis showed that pretreatment anemia ( $p=0.041$ ), pelvic lymph node metastasis ( $p=0.016$ ) and posttreatment SCC-Ag levels ( $p=0.001$ ) were independent prognostic factors for three-year OS. The SCC-Ag level cut-off point for three-year OS rates, calculated using a receiver operating characteristic curve, was 1.15 ng/mL (sensitivity, 80.0%; specificity, 74.0%). **CONCLUSION:** Pretreatment anemia and pelvic lymph node metastasis are poor prognostic factors in locally advanced cervical cancer. Furthermore, posttreatment SCC-Ag levels <1.15 ng/mL predicted better three-year OS rates.

[890]

**TÍTULO / TITLE:** - Factors predicting peritoneal recurrence in advanced gastric cancer: implication for adjuvant intraperitoneal chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gastric Cancer. 2013 Oct 8.

●● Enlace al texto completo (gratis o de pago) [1007/s10120-013-0306-2](#)

**AUTORES / AUTHORS:** - Lee JH; Son SY; Lee CM; Ahn SH; Park DJ; Kim HH

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, Seoul National University Bundang Hospital, 166 Gumi-ro, Bundang-gu, Seongnam-shi, Gyeonggi-do, 463-707, South Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Despite adjuvant chemotherapy, patients with advanced gastric cancer (AGC) often develop recurrence, and the peritoneum is the most common site of recurrence. Therefore, intraperitoneal chemotherapy (IPC) has been proposed as a treatment option. The aim of this study was to select the eligible patients for application of IPC. METHODS: A total of 805 patients with AGC who underwent curative D2 gastrectomy between May 2003 and December 2009 were included in this study. Risk factors for peritoneal recurrence were analyzed. RESULTS: Recurrence developed in 245 patients (30.4 %). The first site of recurrence was the peritoneum in 144 patients (58.8 %), and the 5-year peritoneal recurrence-free survival was 79.3 %. Depth of tumor invasion  $\geq$ T3, extensive lymph node metastasis (N3), Bormann type 4, infiltrative type (Ming's classification), and venous invasion were independent risk factors for peritoneal recurrence. In subgroup analysis with patients who had received adjuvant chemotherapy (n = 481), depth of tumor invasion  $\geq$ T3, Bormann type 4, infiltrative type (Ming's classification), and venous invasion were independent risk factors for peritoneal recurrence. When a peritoneal recurrence risk index was made with each risk factor assigned 1 point (2 points for T4 stage), peritoneal recurrence rates with 0, 1, 2, 3, 4, or 5 points were 0 %, 3.9 %, 13.1 %, 33.3 %, 44.0 %, and 72.0 %, respectively, in those patients. CONCLUSIONS: Patients at higher risk for peritoneal recurrence can be identified from the findings of this study. Further prospective studies are required to evaluate the usefulness of IPC for these patients.

[891]

**TÍTULO / TITLE:** - Thymidylate synthase expression and p21/p53 phenotype of colon cancers identify patients who may benefit from 5-fluorouracil based therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Oncol (Dordr). 2013 Nov 26.

- Enlace al texto completo (gratis o de pago) [1007/s13402-013-0159-z](#)

**AUTORES / AUTHORS:** - Sulzyc-Bielicka V; Domagala P; Bielicki D; Safranow K; Domagala W

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, Pomeranian Medical University, Szczecin, Poland.

**RESUMEN / SUMMARY:** - BACKGROUND: Studies on the expression of thymidylate synthase (TS) in colorectal cancers (CRCs) have failed to provide unequivocal prognostic or predictive information. Here, we assessed the prognostic significance of TS expression in Astler-Coller stage B2 and C CRCs defined by a p21WAF1/p53 immunophenotype in patients subjected to 5-fluorouracil (5FU)-based adjuvant therapy. METHODS: A cohort of 189 CRCs was assessed for TS, p21WAF1 and p53 expression on tissue microarrays using immunohistochemistry, and associations with disease-free survival (DFS) and overall survival (OS) of the patients were assessed using univariate and multivariate analyses. RESULTS: TS expression led to the stratification of patients with colon cancer, but not rectal cancer, with immunophenotypes other than p21WAF1+/p53- (referred to as P&P) into subgroups characterized by a worse (P&P TS+) and a better (P&P TS-) DFS and OS, in univariate

( $P = 0.006$  and  $P = 0.005$ , respectively) and multivariate ( $P = 0.0004$  and  $P = 0.002$ , respectively) analyses. The p21WAF1+/p53- immunophenotype was associated with a favorable prognosis, irrespective of TS expression. CONCLUSIONS: The strong association observed between the P&P TS+ immunophenotype and a worse DFS and OS suggests a predictive significance of TS expression for 5FU-based adjuvant therapy in patients with colon cancers exhibiting the P&P immunophenotype. In addition, our findings suggest that the appropriate target for assessment of TS expression as a prognostic/predictive marker is a subgroup of colon cancers with an immunophenotype other than p21WAF1+/p53-, and that only in this subgroup high TS expression is associated with an unfavorable DFS and OS. Therefore, we suggest that assessing TS expression in conjunction with p21WAF1/p53 immunophenotyping of colon cancers may improve the selection of patients suitable for 5FU-based adjuvant chemotherapy.

[892]

**TÍTULO / TITLE:** - Initiation of aspirin therapy modulates angiogenic protein levels in women with breast cancer receiving tamoxifen therapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Sci. 2013 Oct;6(5):386-90. doi: 10.1111/cts.12070. Epub 2013 May 15.

●● Enlace al texto completo (gratis o de pago) [1111/cts.12070](#)

**AUTORES / AUTHORS:** - Holmes CE; Jasielec J; Levis JE; Skelly J; Muss HB

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, University of Vermont, Burlington, Vermont, USA.

**RESUMEN / SUMMARY:** - Aspirin has a range of antineoplastic properties linked to inhibition of cyclooxygenase enzymes in tumor cells, platelet inhibition and to inhibition of angiogenesis. We undertook a prospective study to determine the influence of a 45-day course of aspirin therapy on circulating and intraplatelet levels of selected proangiogenic (vascular endothelial growth factor [VEGF]) and antiangiogenic (thrombospondin-1 [TSP-1]) proteins, and platelet protein release in women diagnosed with breast cancer who were receiving tamoxifen therapy. Initiation of aspirin therapy increases serum and intraplatelet levels of TSP-1 without a corresponding increase in VEGF levels. Following aspirin therapy, VEGF levels decreased (relative to pretreatment levels) while TSP-1 returned to pretreatment levels. Plasma TSP-1 and VEGF levels did not change on aspirin therapy. Aspirin use also decreased thrombin receptor mediated release of TSP-1 and VEGF from platelets. The selective impact on platelet angiogenic protein content and release supports one mechanism by which aspirin can modify the angiogenic balance in women receiving tamoxifen therapy. Aspirin therapy appears to favor an overall antiangiogenic balance in women with breast cancer who are receiving tamoxifen therapy.

[893]

**TÍTULO / TITLE:** - Glioma IL13Ralpha2 Is Associated with Mesenchymal Signature Gene Expression and Poor Patient Prognosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 18;8(10):e77769. doi: 10.1371/journal.pone.0077769.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0077769](#)

**AUTORES / AUTHORS:** - Brown CE; Warden CD; Starr R; Deng X; Badie B; Yuan YC; Forman SJ; Barish ME

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer Immunotherapy & Tumor Immunology and Hematology & Hematopoietic Cell Transplantation, Beckman Research Institute and City of Hope National Medical Center, Duarte, California, United States of America.

**RESUMEN / SUMMARY:** - A major challenge for successful immunotherapy against glioma is the identification and characterization of validated targets. We have taken a bioinformatics approach towards understanding the biological context of IL-13 receptor alpha2 (IL13Ralpha2) expression in brain tumors, and its functional significance for patient survival. Querying multiple gene expression databases, we show that IL13Ralpha2 expression increases with glioma malignancy grade, and expression for high-grade tumors is bimodal, with approximately 58% of WHO grade IV gliomas over-expressing this receptor. By several measures, IL13Ralpha2 expression in patient samples and low-passage primary glioma lines most consistently correlates with the expression of signature genes defining mesenchymal subclass tumors and negatively correlates with proneural signature genes as defined by two studies. Positive associations were also noted with proliferative signature genes, whereas no consistent associations were found with either classical or neural signature genes. Probing the potential functional consequences of this mesenchymal association through IPA analysis suggests that IL13Ralpha2 expression is associated with activation of proinflammatory and immune pathways characteristic of mesenchymal subclass tumors. In addition, survival analyses indicate that IL13Ralpha2 over-expression is associated with poor patient prognosis, a single gene correlation ranking IL13Ralpha2 in the top ~1% of total gene expression probes with regard to survival association with WHO IV gliomas. This study better defines the functional consequences of IL13Ralpha2 expression by demonstrating association with mesenchymal signature gene expression and poor patient prognosis. It thus highlights the utility of IL13Ralpha2 as a therapeutic target, and helps define patient populations most likely to respond to immunotherapy in present and future clinical trials.

[894]

**TÍTULO / TITLE:** - Decreased Expression of the FOXO3a Gene Is Associated with Poor Prognosis in Primary Gastric Adenocarcinoma Patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 23;8(10):e78158. doi: 10.1371/journal.pone.0078158.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0078158](#)

**AUTORES / AUTHORS:** - Yang XB; Zhao JJ; Huang CY; Wang QJ; Pan K; Wang DD; Pan QZ; Jiang SS; Lv L; Gao X; Chen HW; Yao JY; Zhi M; Xia JC

**INSTITUCIÓN / INSTITUTION:** - State Key Laboratory of Oncology in Southern China and Department of Experimental Research, Sun Yat-sen University Cancer Center, Guangzhou, P.R. China ; Department of Gastroenterology, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, P.R. China.

**RESUMEN / SUMMARY:** - BACKGROUND: FOXO3a, a member of the forkhead class 'O' (FOXO) transcription factor family, controls a wide spectrum of biological processes, such as DNA damage repair, apoptosis, and cell cycle regulation. FOXO3a has been shown to be a tumor suppressor in various cancers. This study investigated

the expression of FOXO3a in primary gastric adenocarcinomas and its prognostic value for primary gastric adenocarcinoma patients. METHODS: Real-time quantitative RT-PCR (qRT-PCR), western blotting, and immunohistochemical staining were used to detect FOXO3a expression in primary gastric cancerous surgical specimens and adjacent non-tumorous tissues. RESULTS: Our data showed that the expression of FOXO3a mRNA ( $p = 0.03$ ) and protein ( $p = 0.019$ ) was lower in cancerous tissues compared with their adjacent non-tumorous tissues. In addition, the chi-square test revealed that low FOXO3a expression was significantly correlated with larger tumor size ( $p = 0.007$ ), poor histopathological classification ( $p = 0.029$ ), depth of invasion ( $p = 0.049$ ), local lymph node metastasis ( $p = 0.013$ ), distant metastasis ( $p = 0.013$ ) and AJCC staging ( $p < 0.001$ ). Kaplan-Meier survival analysis demonstrated that low expression of FOXO3a was significantly correlated with a poor prognosis for gastric cancer patients ( $p < 0.001$ ). The multivariate analysis showed that FOXO3a expression was an independent prognostic factor of the overall survival rate of patients with primary gastric adenocarcinoma. CONCLUSION: Our study suggested that decreased FOXO3a expression may play an important role in the progression of gastric cancer. FOXO3a could be a valuable prognostic marker as well as a potential molecular therapy target for gastric cancer patients.

[895]

**TÍTULO / TITLE:** - Inhibition of protein kinase CK2 with the clinical-grade small ATP-competitive compound CX-4945 or by RNA interference unveils its role in acute myeloid leukemia cell survival, p53-dependent apoptosis and daunorubicin-induced cytotoxicity.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Hematol Oncol. 2013 Oct 12;6(1):78. doi: 10.1186/1756-8722-6-78.

●● Enlace al texto completo (gratis o de pago) [1186/1756-8722-6-78](#)

**AUTORES / AUTHORS:** - Quotti Tubi L; Gurrieri C; Brancalion A; Bonaldi L; Bertorelle R; Manni S; Pavan L; Lessi F; Zambello R; Trentin L; Adami F; Ruzzene M; Pinna LA; Semenzato G; Piazza F

**RESUMEN / SUMMARY:** - BACKGROUND: The involvement of protein kinase CK2 in sustaining cancer cell survival could have implications also in the resistance to conventional and unconventional therapies. Moreover, CK2 role in blood tumors is rapidly emerging and this kinase has been recognized as a potential therapeutic target. Phase I clinical trials with the oral small ATP-competitive CK2 inhibitor CX-4945 are currently ongoing in solid tumors and multiple myeloma. METHODS: We have analyzed the expression of CK2 in acute myeloid leukemia and its function in cell growth and in the response to the chemotherapeutic agent daunorubicin. We employed acute myeloid leukemia cell lines and primary blasts from patients grouped according to the European LeukemiaNet risk classification. Cell survival, apoptosis and sensitivity to daunorubicin were assessed by different means. p53-dependent CK2-inhibition-induced apoptosis was investigated in p53 wild-type and mutant cells. RESULTS: CK2a was found highly expressed in the majority of samples across the different acute myeloid leukemia prognostic subgroups as compared to normal CD34+ hematopoietic and bone marrow cells. Inhibition of CK2 with CX-4945, K27 or siRNAs caused a p53-dependent acute myeloid leukemia cell apoptosis. CK2 inhibition was associated with a synergistic increase of the cytotoxic effects of daunorubicin. Baseline and

daunorubicin-induced STAT3 activation was hampered upon CK2 blockade.  
CONCLUSIONS: These results suggest that CK2 is over expressed across the different acute myeloid leukemia subsets and acts as an important regulator of acute myeloid leukemia cell survival. CK2 negative regulation of the protein levels of tumor suppressor p53 and activation of the STAT3 anti-apoptotic pathway might antagonize apoptosis and could be involved in acute myeloid leukemia cell resistance to daunorubicin.

[896]

**TÍTULO / TITLE:** - Hispolon Induces Apoptosis through JNK1/2-Mediated Activation of a Caspase-8, -9, and -3-Dependent Pathway in Acute Myeloid Leukemia (AML) Cells and Inhibits AML Xenograft Tumor Growth in Vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Agric Food Chem. 2013 Oct 23;61(42):10063-73. doi: 10.1021/jf402956m. Epub 2013 Oct 15.

●● [Enlace al texto completo \(gratis o de pago\) 1021/jf402956m](#)

**AUTORES / AUTHORS:** - Hsiao PC; Hsieh YH; Chow JM; Yang SF; Hsiao M; Hua KT; Lin CH; Chen HY; Chien MH

**INSTITUCIÓN / INSTITUTION:** - School of Medicine, double daggerInstitute of Biochemistry and Biotechnology, and section signInstitute of Medicine, Chung Shan Medical University , No. 110, Section 1, Chien-Kuo N Road, Taichung 40201, Taiwan.

**RESUMEN / SUMMARY:** - Hispolon is an active phenolic compound of *Phellinus igniarius*, a mushroom that was recently shown to have antioxidant and anticancer activities in various solid tumors. Here, the molecular mechanisms by which hispolon exerts anticancer effects in acute myeloid leukemia (AML) cells was investigated. The results showed that hispolon suppressed cell proliferation in the various AML cell lines. Furthermore, hispolon effectively induced apoptosis of HL-60 AML cells through caspases-8, -9, and -3 activations and PARP cleavage. Moreover, treatment of HL-60 cells with hispolon induced sustained activation of JNK1/2, and inhibition of JNK by JNK1/2 inhibitor or JNK1/2-specific siRNA significantly abolished the hispolon-induced activation of the caspase-8/-9/-3. In vivo, hispolon significantly reduced tumor growth in mice with HL-60 tumor xenografts. In hispolon-treated tumors, activation of caspase-3 and a decrease in Ki67-positive cells were observed. Our results indicated that hispolon may have the potential to serve as a therapeutic tool to treat AML.

[897]

**TÍTULO / TITLE:** - Prostate-specific antigen kinetics parameters are predictive of positron emission tomography features worsening in patients with biochemical relapse after prostate cancer treatment with radical intent: Results from a longitudinal cohort study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Scand J Urol. 2013 Nov 21.

●● [Enlace al texto completo \(gratis o de pago\) 3109/21681805.2013.846936](#)

**AUTORES / AUTHORS:** - Gacci M; Cai T; Siena G; Minervini A; Torshizi MF; Bartolini M; Gianni G; Saieva C; Ceroti M; Detti B; Livi L; Pupi A; Carini M

**INSTITUCIÓN / INSTITUTION:** - Department of Urology.

**RESUMEN / SUMMARY:** - Abstract Objective. The aim of this study was to identify prostate-specific antigen (PSA) kinetics parameters predictive of [18F]fluorocholine positron emission tomography/computed tomography (18FC PET/CT) features worsening in a cohort of patients with biochemical failure after prostate cancer treatment. Material and methods. This longitudinal cohort study comprised 103 consecutive patients. All patients underwent two 18FC PET/CT scans: one at baseline (PET1) and one after 6 months (PET2). Total PSA (tPSA), PSA velocity (vPSA), PSA doubling time (PSAdt), absolute variation in PSA values between PET2 and PET1 (DeltaPSA), and percentage variation in PSA between the two PSA measurements (PSA%) were measured in each patient. Progression of disease on 18FC PET/CT findings was compared with the PSA kinetics parameters. The major outcome measure was disease progression at PET2. Results. 18FC PET/CT progression between PET1 and PET2 was reported in 64 patients (62.1%), while in 39 cases it remained unvaried. The following PSA kinetic parameters correlated with worsened 18FC PET/CT findings: DeltaPSA >5 ng/ml [odds ratio (OR = 6.44, 95% confidence interval (CI) 1.04-39.6; p = 0.04], vPSA >6 ng/ml/month (OR = 5.2, 95% CI 0.9-29.8; p = 0.05) and PSAdt <6 months (OR = 5.2, 95% CI 0.4-5.4; p = 0.03). From receiver operating characteristics (ROC) analysis, the combination with the three PSA kinetics parameters for predicting worsened 18FC PET/CT findings resulted in a sensitivity of 86% (95% CI 77-92%) and specificity of 77% (95% CI 65-85%). Conclusion. PSA kinetics is strictly related to 18FC PET/CT findings. In patients with biochemical relapse, DeltaPSA >5 ng/ml, PSAdt <6 months and vPSA >6 ng/ml/month are highly predictive of 18FC PET/CT features worsening, independently from the treatment received.

[898]

**TÍTULO / TITLE:** - Menadione (Vitamin K3) Induces Apoptosis of Human Oral Cancer Cells and Reduces their Metastatic Potential by Modulating the Expression of Epithelial to Mesenchymal Transition Markers and Inhibiting Migration.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):5461-5.

**AUTORES / AUTHORS:** - Suresh S; Raghu D; Karunagaran D

**INSTITUCIÓN / INSTITUTION:** - Department of Biotechnology, Indian Institute of Technology Madras, Chennai, India E-mail : [karuna@iitm.ac.in](mailto:karuna@iitm.ac.in).

**RESUMEN / SUMMARY:** - Oral cancer is one of the most commonly occurring cancers worldwide, decreasing the patient's survival rate due to tumor recurrence and metastasis. Menadione (Vitamin K3) is known to exhibit cytotoxicity in various cancer cells but the present study focused on its effects on viability, apoptosis, epithelial to mesenchymal transition (EMT), anchorage independent growth and migration of oral cancer cells. The results show that menadione is more cytotoxic to SAS (oral squamous carcinoma) cells but not to non-tumorigenic HEK293 and HaCaT cells. Menadione treatment increased the expression of pro-apoptotic proteins, Bax and p53, with a concurrent decrease in anti-apoptotic proteins, Bcl-2 and p65. Menadione induced the expression of E-cadherin but reduced the expression of EMT markers, vimentin and fibronectin. Menadione also inhibited anchorage independent growth and migration in SAS cells. These findings reveal and confirm that menadione is a potential candidate in oral cancer therapy as it exhibits cytotoxic, antineoplastic and antimigratory effects besides effectively blocking EMT in oral cancer cells.

[899]

**TÍTULO / TITLE:** - Tumor cell expression of vascular endothelial growth factor receptor 2 is an adverse prognostic factor in patients with squamous cell carcinoma of the lung.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 14;8(11):e80292. doi: 10.1371/journal.pone.0080292.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0080292](#)

**AUTORES / AUTHORS:** - Holzer TR; Fulford AD; Nedderman DM; Umberger TS; Hozak RR; Joshi A; Melemed SA; Benjamin LE; Plowman GD; Schade AE; Ackermann BL; Konrad RJ; Nasir A

**INSTITUCIÓN / INSTITUTION:** - Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, United States of America.

**RESUMEN / SUMMARY:** - A robust immunohistochemical (IHC) assay for VEGFR2 was developed to investigate its utility for patient tailoring in clinical trials. The sensitivity, specificity, and selectivity of the IHC assay were established by siRNA knockdown, immunoblotting, mass spectrometry, and pre-absorption experiments. Characterization of the assay included screening a panel of multiple human cancer tissues and an independent cohort of non-small cell lung carcinoma (NSCLC, n = 118) characterized by TTF-1, p63, CK5/6, and CK7 IHC. VEGFR2 immunoreactivity was interpreted qualitatively (VEGFR2 positive/negative) in blood vessels and by semi-quantitative evaluation using H-scores in tumor cells (0-300). Associations were determined among combinations of VEGFR2 expression in blood vessels and tumor cells, and clinico-pathologic characteristics (age, sex, race, histologic subtype, disease stage) and overall survival using Kaplan-Meier analyses and appropriate statistical models. VEGFR2 expression both in blood vessels and in tumor cells in carcinomas of the lung, cervix, larynx, breast, and others was demonstrated. In the validation cohort, 99/118 (83.9%) NSCLC tissues expressed VEGFR2 in the blood vessels and 46/118 (39.0%) showed high tumor cell positivity (H-score  $\geq 10$ ). Vascular and tumor cell expression were inversely correlated (p = 0.0175). High tumor cell expression of VEGFR2 was associated with a 3.7-fold reduction in median overall survival in lung squamous-cell carcinoma (SCC, n = 25, p = 0.0134). The inverse correlation between vascular and tumor cell expression of VEGFR2 and the adverse prognosis associated with high VEGFR2 expression in immunohistochemically characterized pulmonary SCC are new findings with potential therapeutic implications. The robustness of this novel IHC assay will support further evaluation of its utility for patient tailoring in clinical trials of antiangiogenic agents.

[900]

**TÍTULO / TITLE:** - Epigenetics targeted protein-vorinostat nanomedicine inducing apoptosis in heterogeneous population of primary acute myeloid leukemia cells including refractory and relapsed cases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Nanomedicine. 2013 Oct 5. pii: S1549-9634(13)00542-X. doi: 10.1016/j.nano.2013.09.008.

●● Enlace al texto completo (gratis o de pago) [1016/j.nano.2013.09.008](#)

**AUTORES / AUTHORS:** - Chandran P; Kavalakatt A; Malarvizhi GL; Vasanthakumari DR; Retnakumari AP; Sidharthan N; Pavithran K; Nair S; Koyakutty M

**INSTITUCIÓN / INSTITUTION:** - Amrita Centre for Nanosciences and Molecular Medicine, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala, India.

**RESUMEN / SUMMARY:** - Aberrant epigenetics play a key role in the onset and progression of acute myeloid leukemia (AML). Herein we report in silico modelling based development of a novel, protein-vorinostat nanomedicine exhibiting selective and superior anti-leukemic activity against heterogeneous population of AML patient samples (n=9), including refractory and relapsed cases, and three representative cell lines expressing CD34+/CD38- stem cell phenotype (KG-1a), promyelocytic phenotype (HL-60) and FLT3-ITD mutation (MV4-11). Nano-vorinostat having ~100nm size exhibited enhanced cellular uptake rendering significantly lower IC50 in AML cell lines and patient samples, and induced enhanced HDAC inhibition, oxidative injury, cell cycle arrest and apoptosis compared to free vorinostat. Most importantly, nanomedicine showed exceptional single-agent activity against the clonogenic proliferative capability of bone marrow derived leukemic progenitors, while remaining non-toxic to healthy bone marrow cells. Collectively, this epigenetics targeted nanomedicine appears to be a promising therapeutic strategy against various French-American-British (FAB) classes of AML.

[901]

**TÍTULO / TITLE:** - Evaluating predictive pharmacogenetic signatures of adverse events in colorectal cancer patients treated with fluoropyrimidines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 22;8(10):e78053. doi: 10.1371/journal.pone.0078053.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0078053](#)

**AUTORES / AUTHORS:** - Jennings BA; Loke YK; Skinner J; Keane M; Chu GS; Turner R; Epurescu D; Barrett A; Willis G

**INSTITUCIÓN / INSTITUTION:** - Norwich Medical School, University of East Anglia, Norwich, United Kingdom.

**RESUMEN / SUMMARY:** - The potential clinical utility of genetic markers associated with response to fluoropyrimidine treatment in colorectal cancer patients remains controversial despite extensive study. Our aim was to test the clinical validity of both novel and previously identified markers of adverse events in a broad clinical setting. We have conducted an observational pharmacogenetic study of early adverse events in a cohort study of 254 colorectal cancer patients treated with 5-fluorouracil or capecitabine. Sixteen variants of nine key folate (pharmacodynamic) and drug metabolising (pharmacokinetic) enzymes have been analysed as individual markers and/or signatures of markers. We found a significant association between TYMP S471L (rs11479) and early dose modifications and/or severe adverse events (adjusted OR = 2.02 [1.03; 4.00], p = 0.042, adjusted OR = 2.70 [1.23; 5.92], p = 0.01 respectively). There was also a significant association between these phenotypes and a signature of DPYD mutations (Adjusted OR = 3.96 [1.17; 13.33], p = 0.03, adjusted OR = 6.76 [1.99; 22.96], p = 0.002 respectively). We did not identify any significant associations between the individual candidate pharmacodynamic markers and toxicity. If a predictive test for early adverse events analysed the TYMP and DPYD variants as a signature, the sensitivity would be 45.5 %, with a positive predictive value of just 33.9 % and thus poor clinical validity. Most studies to date have been under-powered

to consider multiple pharmacokinetic and pharmacodynamic variants simultaneously but this and similar individualised data sets could be pooled in meta-analyses to resolve uncertainties about the potential clinical utility of these markers.

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[902]

**TÍTULO / TITLE:** - C-terminal tensin-like protein is a novel prognostic marker for primary melanoma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 7;8(11):e80492. doi: 10.1371/journal.pone.0080492.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0080492](#)

**AUTORES / AUTHORS:** - Sjoestroem C; Khosravi S; Zhang G; Martinka M; Li G

**INSTITUCIÓN / INSTITUTION:** - Department of Dermatology and Skin Science, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.

**RESUMEN / SUMMARY:** - BACKGROUND: C-terminal tensin-like protein (Cten) is a focal adhesion protein originally identified as a tumor suppressor in prostate cancer. It has since been found to be overexpressed and function as an oncogene in numerous other cancers, but the expression status of Cten in melanoma is still unknown. METHODS: Using tissue microarrays containing 562 melanocytic lesions, we evaluated Cten protein expression by immunohistochemistry. The association between Cten expression and patient survival was examined using Kaplan-Meier survival analysis, and univariate and multivariate Cox regression analyses were used to estimate the crude and adjusted hazard ratios. RESULTS: Strong Cten expression was detected in 7%, 24%, 41%, and 46% of normal nevi, dysplastic nevi, primary melanoma, and metastatic melanoma samples, respectively, and Cten expression was found to be significantly higher in dysplastic nevi compared to normal nevi ( $P = 0.046$ ), and in primary melanoma compared to dysplastic nevi ( $P = 0.003$ ), but no difference was observed between metastatic and primary melanoma. Cten staining also correlated with AJCC stages ( $P = 0.015$ ) and primary tumor thickness ( $P = 0.002$ ), with Cten expression being induced in the transition from thin ( $<1\text{mm}$ ) to thick ( $\geq 1\text{mm}$ ) melanomas. Strong Cten expression was significantly associated with a worse 5-year overall ( $P = 0.008$ ) and disease-specific survival ( $P = 0.004$ ) for primary melanoma patients, and multivariate Cox regression analysis revealed that Cten expression was an independent prognostic marker for these patients ( $P = 0.038$  for overall survival;  $P = 0.021$  for disease-specific survival). CONCLUSION: Our findings indicate that induction of Cten protein expression is a relatively early event in melanoma progression, and that Cten has the potential to serve as a prognostic marker for primary melanoma patients.

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[903]

**TÍTULO / TITLE:** - Adverse events of tumor necrosis factor inhibitors.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Dig Dis. 2013;31(3-4):374-8. doi: 10.1159/000354703. Epub 2013 Nov 14.

●● Enlace al texto completo (gratis o de pago) [1159/000354703](#)

**AUTORES / AUTHORS:** - Fellermann K

**INSTITUCIÓN / INSTITUTION:** - Division of Gastroenterology, Department of Internal Medicine I, University Hospital of Schleswig-Holstein, Lubeck, Germany.

**RESUMEN / SUMMARY:** - Background/Aims: Adverse events in anti-TNF treatment can be divided into allergic reactions with an acute and delayed onset, infectious complications in relation to the underlying disease, and without. Last but not least, there is the unresolved question of tumor induction and propagation. All of these may account for morbidity and eventually mortality. Methods: Literature-based review to update current knowledge about safety and adverse events of TNF blockers. Results: Major drawbacks are infectious complications with the use of anti-TNF-alpha antibodies. The risk is increased in inflammatory bowel disease in general and in the perioperative setting of Crohn's disease patients. The number of tuberculosis cases has decreased since meticulous testing prior to treatment start is mandatory. An excess mortality that has been reported from referral centers is neither documented in randomized controlled trials nor in real-life settings. Regarding malignancies, lymphoma and skin cancer are a concern. The incidence of lymphoma may be raised, but this has also been debated with the use of thiopurines. Skin cancer, especially melanoma, is more common in inflammatory bowel disease and may be associated with the use of biologics. Overall, most studies do not address the influence of active inflammation or co-administration of other drugs. Hence, the risk attributable to TNF blockers alone is currently ill-defined. Conclusion: Treatment with anti-TNF-alpha antibodies is an option with substantial risks. Most problems can be prevented by thorough workup of the patient. © 2013 S. Karger AG, Basel.

[904]

**TÍTULO / TITLE:** - Elevated pre-treatment levels of high sensitivity C-reactive protein as a potential prognosticator in patients with colorectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Ther Med. 2013 Dec;6(6):1369-1374. Epub 2013 Oct 16.

●● [Enlace al texto completo \(gratis o de pago\) 3892/etm.2013.1350](#)

**AUTORES / AUTHORS:** - Lin M; Huang J; Zhu J; Shen H

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology, Taizhou People's Hospital, Taizhou, Jiangsu 225300, P.R. China.

**RESUMEN / SUMMARY:** - Elevated levels of C-reactive protein (CRP) have been described as a prognostic factor in various types of human malignancy. In the present study, the prognostic potency of CRP was validated for patients with colorectal cancer (CRC) in order to guide patient management and define high-risk populations for follow-up or for therapeutic purposes. The association between the high sensitivity-CRP (hs-CRP) levels of a total of 123 patients with CRC and their clinicopathological characteristics was explored. Subsequently, univariate and multivariate analyses were performed to investigate the survival impact of pre-treatment hs-CRP levels in this cohort study. Statistically significant correlations between the serum levels of hs-CRP and lymph node and distant metastasis ( $P < 0.001$  and  $P = 0.012$ , respectively), vascular and perineural invasion ( $P < 0.001$  and  $P < 0.001$ ), grades ( $P = 0.022$ ) and clinical stages ( $P = 0.001$ ), but not age and gender ( $P = 0.616$  and  $0.676$ , respectively), were found. The five-year survival rate of patients with elevated ( $> 5.0$  mg/l) hs-CRP levels was demonstrated to be significantly less than that of those in the normal group ( $\geq 5.0$  mg/l) by applying the Kaplan-Meier method (13.3 versus 57.0%, log-rank test  $P < 0.001$ ). Furthermore, following identification as a prognostic factor through using univariate analysis, high levels of hs-CRP ( $P < 0.001$ ) were validated as an independent

prognosticator in CRC in the present study through using multivariate analysis. Pre-treatment serum CRP levels were associated with advanced and progressed CRC patients, therefore these levels may serve as a potential prognostic marker for CRC patients.

[905]

**TÍTULO / TITLE:** - Expression of nerve growth factor and heme oxygenase-1 predict poor survival of breast carcinoma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Nov 1;13(1):516.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-516](#)

**AUTORES / AUTHORS:** - Noh SJ; Bae JS; Jamiyandorj U; Park HS; Kwon KS; Jung SH; Youn HJ; Lee H; Park BH; Chung MJ; Moon WS; Kang MJ; Jang KY

**RESUMEN / SUMMARY:** - BACKGROUND: Nerve growth factor (NGF) is a neurotrophin and has been suggested to induce heme oxygenase-1 (HO1) expression. Although the role of HO1 in tumorigenesis remains controversial, recent evidence suggests NGF and HO1 as tumor-progressing factors. However, the correlative role of NGF and HO1 and their prognostic impact in breast carcinoma is unknown. METHODS: We investigated the expression and prognostic significance of the expression of NGF and HO1 in 145 cases of breast carcinoma. RESULTS: Immunohistochemical expression of NGF and HO1 was observed in 31% and 49% of breast carcinoma, respectively. The expression of NGF and HO1 significantly associated with each other, and both have a significant association with histologic grade, HER2 expression, and latent distant metastasis. The expression of NGF and HO1 predicted shorter overall survival of breast carcinoma by univariate and multivariate analysis. NGF expression was an independent prognostic indicator for relapse-free survival by multivariate analysis. The combined expression pattern of NGF and HO1 was also an independent prognostic indicator of overall survival and relapse-free survival. The patients with tumors expressing NGF had the shortest survival and the patients with tumor, which did not express NGF or HO1 showed the longest survival time. CONCLUSIONS: This study has demonstrated that individual expression of NGF or HO1, and the combined NGF/HO1 expression pattern could be prognostic indicators for breast carcinoma patients.

[906]

**TÍTULO / TITLE:** - Confirmation of -174G/C interleukin-6 gene promoter polymorphism as a genetic marker predicting antitumor necrosis factor treatment outcome.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Pharmacogenet Genomics. 2013 Nov 18.

●● Enlace al texto completo (gratis o de pago)

[1097/FPC.0000000000000013](#)

**AUTORES / AUTHORS:** - Davila-Fajardo CL; Marquez A; Pascual-Salcedo D; Moreno Ramos MJ; Garcia-Portales R; Magro C; Alegre-Sancho JJ; Balsa A; Cabeza-Barrera J; Raya E; Martin J

**INSTITUCIÓN / INSTITUTION:** - aInstituto de Parasitología y Biomedicina Lopez-Neyra, CSIC bDepartment of Clinical Pharmacy, UGC Farmacia Granada cDepartment of Rheumatology, Instituto de Investigacion Biosanitaria de Granada, San Cecilio University Hospital, Granada Departments of dImmunology eRheumatology, IdiPAZ,

RIER, La Paz University Hospital, Madrid fDepartment of Rheumatology, Virgen de la Arrixaca University Hospital, Murcia gDepartment of Rheumatology, Virgen de la Victoria University Hospital, Malaga hDepartment of Rheumatology, Doctor Peset Hospital, Valencia, España.

**RESUMEN / SUMMARY:** - BACKGROUND: The IL-6 -174G/C genetic variant has recently been associated with the clinical response to etanercept therapy in rheumatoid arthritis (RA) patients. Considering previous results, the aim of our study was to validate the role of this polymorphism as a predictor of the antitumor necrosis factor (anti-TNF) treatment outcome in RA. MATERIALS AND METHODS: Our study population was composed of 199 Spanish patients with RA receiving anti-TNF therapy. The IL-6 -174G/C (rs1800795) genetic variant was genotyped using the TaqMan allelic discrimination technology. Patients were classified, according to the European League Against Rheumatism (EULAR) criteria, as responders (good and moderate response) and nonresponders at 6, 12, 18, and 24 months after the first infusion. RESULTS: The -174\*G allele was significantly associated with a good or moderate EULAR response at 12 [P=0.015, odds ratio (OR)=2.93, 95% confidence interval (CI) 1.29-6.70], 18 (P=4.54E-03, OR=5.17, 95% CI 1.80-14.85), and 24 months (P=4.54E-03, OR=14.86, 95% CI 2.91-75.91). A meta-analysis combining these data with the results from a previous study confirmed this association (P=1.89E-02, OR=1.80, 95% CI 1.13-2.87, at 12 months). CONCLUSION: Our results support the role of the -174G/C IL-6 polymorphism as a genetic marker of responsiveness to anti-TNF therapy.

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[907]

**TÍTULO / TITLE:** - A single nucleotide polymorphism in EZH2 predicts overall survival rate in patients with cholangiocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Nov;6(5):1487-1491. Epub 2013 Sep 2.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ol.2013.1559](#)

**AUTORES / AUTHORS:** - Paolicchi E; Pacetti P; Giovannetti E; Mambrini A; Orlandi M; Crea F; Romani AA; Tartarini R; Danesi R; Peters GJ; Cantore M

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Division of Pharmacology, University of Pisa, Pisa I-56126, Italy.

**RESUMEN / SUMMARY:** - Cholangiocarcinoma (CCA) is a deadly disease arising from the malignant transformation of cholangiocytes. Enhancer of zeste homolog 2 (EZH2) is overexpressed in poorly differentiated CCA. Functional single nucleotide polymorphisms (SNPs) in this gene may affect the role of EZH2 in cholangiocarcinogenesis and chemoresistance. The aim of the current study was to evaluate the correlation between EZH2 SNPs and clinical outcome. Using PROMO3.0, GeneCard and MicroSNiper, 4 EZH2 SNPs with functional relevance in CCA were selected in silico. These SNPs were studied in genomic DNA extracted from the blood samples of 75 patients with advanced CCA, who were treated with epirubicin-cisplatin-xeloda (ECX regimen). SNP genotyping was performed with specific PCR assays. The rs887569 TT genotype was correlated with a significantly longer overall survival (OS; TT vs. CT-CC, P=0.026). Moreover, the TT genotype revealed a trend toward a significant association with a reduced risk of mortality (HR, 0.59; 95% CI, 0.33-1.05; P=0.075), by multivariate analysis. These results support future studies on the role of rs887569 EZH2 SNP as a possible predictive marker of OS in advanced CCA patients.

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[908]

**TÍTULO / TITLE:** - Reversion effects of curcumin on multidrug resistance of MNNG/HOS human osteosarcoma cells in vitro and in vivo through regulation of P-glycoprotein.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin Med J (Engl). 2013 Nov;126(21):4116-23.

**AUTORES / AUTHORS:** - Si M; Zhao J; Li X; Tian JG; Li YG; Li JM

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopedics, Qilu Hospital of Shandong University, Jinan, Shandong 250012, China.

**RESUMEN / SUMMARY:** - BACKGROUND: P-glycoprotein (P-gp) encoded by ATP-binding cassette sub-family B member 1 (ABCB1) gene is a kind of ATP-dependent drug transporter, which plays important roles in multidrug resistance (MDR) of human cancers, such as osteosarcoma. Curcumin is a natural phenolic coloring compound originating from the rhizomes of *Curcuma longa*, which is proved to possess antitumor biological activities including reversion of MDR. However, the effect and molecular mechanisms of curcumin to osteosarcoma MDR remain unclear. METHODS: We established a human osteosarcoma drug-resistant cell line MNNG/HOS/MTX by pulse exposure to methotrexate (MTX) and verified that the new cell lines were cross-resistant to other anticancer agents. Then, according to the cytotoxicity assay, we reversed MDR of MNNG/HOS/MTX by 30 micromol/L curcumin, and detected the mechanisms of curcumin reversing MDR through Real-time PCR, Western blotting assay, and Rhodamine123 (Rh123) transport test. Finally, we evaluated the effect of curcumin reversing MDR in vivo by MNNG/HOS/MTX cells xenograft-nude mice model. RESULTS: MNNG/HOS/MTX was proved to be a human osteosarcoma MDR cell line. MTT tumor chemosensitivity test indicates that 30 micromol/L curcumin attenuates the half maximal inhibitory concentration (IC<sub>50</sub>) and resistance index (RI) to MTX, diamminedichloroplatinum (DDP), adriamycin (ADM), ifosfamide (IFO), and epirubicin (EPI) in MNNG/HOS/MTX cells ( $P < 0.05$ ). Real-time PCR and Western blotting assays demonstrated that curcumin down-regulated P-gp expression of MNNG/HOS/MTX cells. Rh123 transport test showed that curcumin inhibited the transport function of P-gp in vitro. In vivo studies showed that curcumin displayed the features of sensitizing antitumor drugs and inhibiting the proliferation, invasion, and metastasis of osteosarcoma MDR cells. CONCLUSION: Down-regulation of P-gp and inhibition of the function of P-gp efflux pump may contribute to MDR reversion induced by curcumin in vitro and in vivo.

[909]

**TÍTULO / TITLE:** - Efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors for Chinese patients with squamous cell carcinoma of lung harboring mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Thorac Dis. 2013 Oct;5(5):585-592.

●● [Enlace al texto completo \(gratis o de pago\) 3978/j.issn.2072-](#)

[1439.2013.09.15](#)

**AUTORES / AUTHORS:** - Fang W; Zhang J; Liang W; Huang Y; Yan Y; Wu X; Hu Z; Ma Y; Zhao H; Zhao Y; Yang Y; Xue C; Zhang J; Zhang L

**INSTITUCIÓN / INSTITUTION:** - Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine Guangzhou 510060, China;

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Epidermal growth factor receptor (EGFR) mutation mostly occurred in lung adenocarcinoma, rarely in squamous cell carcinoma (SQCC). EGFR mutation rate in SQCC varied in previous reports, and the efficacy of EGFR tyrosine kinase inhibitors (TKIs) in SQCC harboring EGFR mutation has not yet been fully evaluated. The aim of this study was to investigate the efficacy EGFR-TKIs for Chinese patients with SQCC of lung harboring EGFR mutation. **PATIENTS AND METHODS:** Two cohorts of patients were analyzed. The first cohort included 146 consecutive post-operation SQCC patients from January 2008 to October 2012. The second cohort included 63 patients with advanced SQCC receiving EGFR-TKIs treatment. EGFR mutation analysis was performed with Real-time PCR method. The pathologic diagnosis was validated with immunohistochemistry (IHC) for patients harboring activated EGFR mutation. And the efficacy of EGFR-TKIs in squamous cell carcinoma of lung (SQCC) was evaluated in patients with activated EGFR mutations. **RESULTS:** In the first cohort, 146 resected patients, EGFR mutations were detected in 3 patients, with the mutation rate of 2.0%. In cohort two, 63 patients treated with EGFR-TKIs, 15 patients possessed activated EGFR mutations. The response rate and disease control rate in these patients was 26.7% and 66.7% respectively. 5 patients had disease control over 6 months. The progression free survival (PFS) in EGFR-mutated patients was 3.9 months. **CONCLUSIONS:** In Chinese SQCC patients, EGFR mutation rate was extremely low. EGFR-TKIs seemed to be less effective in EGFR-mutated SQCC patients, but some patients could still obtain benefit from EGFR-TKIs. To identify this part of patients, further study was warranted in the future.

[910]

**TÍTULO / TITLE:** - High imatinib dose overcomes insufficient response associated with ABCG2 haplotype in chronic myelogenous leukemia patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncotarget. 2013 Oct;4(10):1582-91.

**AUTORES / AUTHORS:** - Delord M; Rousselot P; Cayuela JM; Sigaux F; Guilhot J; Preudhomme C; Guilhot F; Loiseau P; Raffoux E; Geromin D; Genin E; Calvo F; Bruzzoni-Giovanelli H

**INSTITUCIÓN / INSTITUTION:** - Plateforme de Bioinformatique et Biostatistique, Institut Universitaire d'Hematologie, Universite Paris Diderot, Sorbonne Paris Cite.

**RESUMEN / SUMMARY:** - Pharmacogenetic studies in chronic myelogenous leukemia (CML) typically use a candidate gene approach. In an alternative strategy, we analyzed the impact of single nucleotide polymorphisms (SNPs) in drug transporter genes on the molecular response to imatinib, using a DNA chip containing 857 SNPs covering 94 drug transporter genes. Two cohorts of CML patients treated with imatinib were evaluated: an exploratory cohort including 105 patients treated at 400 mg/d and a validation cohort including patients sampled from the 400 mg/d and 600 mg/d arms of the prospective SPIRIT trial (n=239). Twelve SNPs discriminating patients according to cumulative incidence of major molecular response (CI-MMR) were identified within the exploratory cohort. Three of them, all located within the ABCG2 gene, were validated in patients included in the 400 mg/d arm of the SPIRIT trial. We identified an ABCG2 haplotype (define as G-G, rs12505410 and rs2725252) as associated with significantly

higher CI-MMR in patients treated at 400 mg/d. Interestingly, we found that patients carrying this ABCG2 “favorable” haplotype in the 400 mg arm reached similar CI-MMR rates that patients randomized in the imatinib 600 mg/d arm. Our results suggest that response to imatinib may be influenced by constitutive haplotypes in drug transporter genes. Lower response rates associated with “non- favorable” ABCG2 haplotypes may be overcome by increasing the imatinib daily dose up to 600 mg/d.

[911]

**TÍTULO / TITLE:** - Selective antitumor effect of neural stem cells expressing cytosine deaminase and interferon-beta against ductal breast cancer cells in cellular and xenograft models.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Stem Cell Res. 2013 Oct 1;12(1):36-48. doi: 10.1016/j.scr.2013.09.010.

●● Enlace al texto completo (gratis o de pago) [1016/j.scr.2013.09.010](#)

**AUTORES / AUTHORS:** - Yi BR; Hwang KA; Aboody KS; Jeung EB; Kim SU; Choi KC

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Veterinary Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

**RESUMEN / SUMMARY:** - Due to their inherent tumor-tropic properties, genetically engineered stem cells may be advantageous for gene therapy treatment of various human cancers, including brain, liver, ovarian, and prostate malignancies. In this study, we employed human neural stem cells (HB1.F3; hNSCs) transduced with genes expressing Escherichia coli cytosine deaminase (HB1.F3.CD) and human interferon-beta (HB1.F3.CD.IFN-beta) as a treatment strategy for ductal breast cancer. CD can convert the prodrug 5-fluorocytosine (5-FC) to its active chemotherapeutic form, 5-fluorouracil (5-FU), which induces a tumor-killing effect through DNA synthesis inhibition. IFN-beta also strongly inhibits tumor growth by the apoptotic process. RT-PCR confirmed that HB1.F3.CD cells expressed CD and HB1.F3.CD.IFN-beta cells expressed both CD and IFN-beta. A modified transwell migration assay showed that HB1.F3.CD and HB1.F3.CD.IFN-beta cells selectively migrated toward MCF-7 and MDA-MB-231 human breast cancer cells. In hNSC-breast cancer co-cultures the viability of breast cancer cells which were significantly reduced by HB1.F3.CD or HB1.F3.CD.IFN-beta cells in the presence of 5-FC. The tumor inhibitory effect was greater with the HB1.F3.CD.IFN-beta cells, indicating an additional effect of IFN-beta to 5-FU. In addition, the tumor-tropic properties of these hNSCs were found to be attributed to chemoattractant molecules secreted by breast cancer cells, including stem cell factor (SCF), c-kit, vascular endothelial growth factor (VEGF), and VEGF receptor 2. An in vivo assay performed using MDA-MB-231/luc breast cancer mammary fat pad xenografts in immunodeficient mice resulted in 50% reduced tumor growth and increased long-term survival in HB1.F3.CD and HB1.F3.CD.IFN-beta plus 5-FC treated mice relative to controls. Our results suggest that hNSCs genetically modified to express CD and/or IFN-beta genes can be used as a novel targeted cancer gene therapy.

[912]

**TÍTULO / TITLE:** - SIRT1 Expression Is Associated with the Chemotherapy Response and Prognosis of Patients with Advanced NSCLC.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 5;8(11):e79162. doi: 10.1371/journal.pone.0079162.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0079162](#)

**AUTORES / AUTHORS:** - Zhang T; Rong N; Chen J; Zou C; Jing H; Zhu X; Zhang W

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiovascular Surgery, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, Shandong Province, China.

**RESUMEN / SUMMARY:** - AIM: The role of Sirtuin 1 (SIRT 1) in carcinogenesis is controversial. This study was to explore the association between the SIRT1 expression and the clinical characteristics, the responsiveness to chemotherapy and prognosis in Non-small cell lung cancer (NSCLC). METHODS: We enrolled 295 patients with inoperable advanced stage of NSCLC, namely, stage III (A+B) and IV NSCLC. All patients had received platinum-based chemotherapy after diagnosis and the chemotherapy response were evaluated. All patients were followed up for overall survival (OS) and progression free survival (PFS). In vitro, H292 cells were transfected with SIRT1 small interfering RNA (siRNA). The cell biological behaviors and chemosensitivity to cisplatin treatment were studied. The in vivo tumorigenesis and metastasis assays were performed in nude mice. RESULTS: We found that the SIRT1 expressions were significantly associated with the tumor stage, tumor size and differentiation status. Patients with high SIRT 1 expressions had a significantly higher chance to be resistant to chemotherapy than those with low SIRT 1 expression. Patients with high expression of SIRT1 had significantly shorter OS and DFS than those with low expression. Cox analyses confirmed that the SIRT 1 expression was a strong predictor for a poor OS and PFS in NSCLC patients underwent Platinum-based chemotherapy. In vitro studies revealed that the reduced expression SIRT 1 by siRNA technique significantly inhibited cell proliferation, migration and invasion. More importantly, SIRT1 si-RNA significantly enhanced the chemosensitivity of H292 cells to cisplatin treatment. The in vivo tumorigenesis and metastasis assays showed that SIRT1 knockdown dramatically reduced the tumor volume and the metastatic ability in nude mice. CONCLUSION: Collectively, our data suggest that the SIRT1 expression may be a molecular marker associated with the NSCLC clinical features, treatment responsiveness and prognosis of advanced NSCLC.

[913]

**TÍTULO / TITLE:** - Increased expression of alpha5beta1-integrin is a prognostic marker for patients with gastric cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Nov 19.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1133-y](#)

**AUTORES / AUTHORS:** - Ren J; Xu S; Guo D; Zhang J; Liu S

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Shenzhen Futian Hospital Affiliated to Guangdong Medical College, 3025 Shennan Middle Road, Shenzhen, 518029, Guangdong, People's Republic of China.

**RESUMEN / SUMMARY:** - OBJECTIVE: The study was to evaluate the association of expression level of alpha5beta1-integrin with clinicopathologic features and prognosis in gastric cancer (GC). METHODS: The expression of alpha5beta1-integrin in normal gastric mucosa and GC tissue was detected with immunohistochemistry. The level of

alpha5 and beta1 mRNA in GC tissues and non-neoplastic tissues was evaluated in 48 paired cases by quantitative real-time polymerase chain reaction (qRT-PCR). Survival analysis by the Kaplan-Meier method was performed to assess prognostic significance. RESULTS: The alpha5beta1-integrin expression was detected in 68.3 % (127/186) GC samples, and there was a significant difference on their positive expression rate between GC tissue and normal gastric mucosa ( $P < 0.001$ ). The positive expression rate of alpha5beta1-integrin in patients with poor histologic differentiation ( $P = 0.001$ ), lymph node metastasis ( $P < 0.001$ ), and recurrence ( $P < 0.001$ ) group was heightened. Using Kaplan-Meier analysis, a comparison of survival curves of low versus high expresser of alpha5beta1-integrin revealed a highly significant difference in human GC tissue ( $P = 0.002$ ), which suggested that overexpression of alpha5beta1-integrin is associated with a worse prognosis. Multivariate analyses showed that alpha5beta1-integrin expression was independent risk factor predicting overall survival [Hazard ratio (HR) 1.594, 95 % confidence interval (CI) 1.236-2.408,  $P = 0.006$ ] and disease-free survival [HR 3.952, 95 % CI 1.676-9.861,  $P = 0.003$ ] in GC. CONCLUSIONS: The alpha5beta1-integrin promotes angiogenesis and associates with lymph node metastasis, vascular invasion and poor prognosis of GC. The current study shows that alpha5beta1-integrin may be an independent prognostic factor for GC patients.

[914]

**TÍTULO / TITLE:** - Analyses of potential predictive markers and survival data for a response to sunitinib in patients with metastatic renal cell carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Sep 27;8(9):e76386. doi: 10.1371/journal.pone.0076386.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0076386](#)

**AUTORES / AUTHORS:** - Dornbusch J; Zacharis A; Meinhardt M; Erdmann K; Wolff I; Froehner M; Wirth MP; Zastrow S; Fuessel S

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, Dresden University of Technology, Dresden, Germany.

**RESUMEN / SUMMARY:** - BACKGROUND: Patients with metastatic clear cell renal cell carcinoma (ccRCC) are frequently treated with tyrosine kinase inhibitors (TKI) such as sunitinib. It inhibits angiogenic pathways by mainly targeting the receptors of VEGF and PDGF. In ccRCC, angiogenesis is characterized by the inactivation of the von Hippel-Lindau gene (VHL) which in turn leads to the induction of HIF1alpha target genes such as CA9 and VEGF. Furthermore, the angiogenic phenotype of ccRCC is also reflected by endothelial markers (CD31, CD34) or other tumor-promoting factors like Ki67 or survivin. METHODS: Tissue microarrays from primary tumor specimens of 42 patients with metastatic ccRCC under sunitinib therapy were immunohistochemically stained for selected markers related to angiogenesis. The prognostic and predictive potential of these markers was assessed on the basis of the objective response rate which was evaluated according to the RECIST criteria after 3, 6, 9 months and after last report (12-54 months) of sunitinib treatment. Additionally, VHL copy number and mutation analyses were performed on DNA from cryo-preserved tumor tissues of 20 ccRCC patients. RESULTS: Immunostaining of HIF-1alpha, CA9, Ki67, CD31, pVEGFR1, VEGFR1 and -2, pPDGFRalpha and -beta was significantly associated with the sunitinib response after 6 and 9 months as well as last report under therapy.

Furthermore, HIF-1alpha, CA9, CD34, VEGFR1 and -3 and PDGFRalpha showed significant associations with progression-free survival (PFS) and overall survival (OS). In multivariate Cox proportional hazards regression analyses high CA9 membrane staining and a response after 9 months were independent prognostic factors for longer OS. Frequently observed copy number loss and mutation of VHL gene lead to altered expression of VHL, HIF-1alpha, CA9, and VEGF. CONCLUSIONS: Immunoexpression of HIF-1alpha, CA9, Ki67, CD31, pVEGFR1, VEGFR1 and -2, pPDGFRalpha and -beta in the primary tumors of metastatic ccRCC patients might support the prediction of a good response to sunitinib treatment.

[915]

**TÍTULO / TITLE:** - Complete Response to Trastuzumab-Based Chemotherapy in a Patient with Human Epidermal Growth Factor Receptor-2-Positive Metastatic Salivary Duct Carcinoma ex Pleomorphic Adenoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Case Rep Oncol. 2013 Sep 10;6(3):450-5. doi: 10.1159/000355219.

●● Enlace al texto completo (gratis o de pago) [1159/000355219](#)

**AUTORES / AUTHORS:** - Kadowaki S; Yatabe Y; Hirakawa H; Komori A; Kondoh C; Hasegawa Y; Muro K

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan.

**RESUMEN / SUMMARY:** - INTRODUCTION: Carcinoma ex pleomorphic adenoma (CXPA) of the salivary glands has often a salivary duct carcinoma (SDC) component, which resembles ductal carcinoma of the breast and frequently overexpresses human epidermal growth factor receptor-2 (HER2). We report a case of metastatic CXPA with SDC component who was treated with trastuzumab-based chemotherapy and has had a durable complete response. CASE REPORT: A 74-year-old man was diagnosed with CXPA of the right parotid gland. The resected tumor was histologically diagnosed as CXPA with a predominant SDC component that showed strong positivity for HER2 protein and HER2 gene amplification. Multiple pulmonary metastatic lesions were detected after surgery, and combination chemotherapy with paclitaxel and trastuzumab was initiated. A complete response was confirmed after 7 treatment cycles, and no evidence of disease progression has been observed after 13 months of initiation of therapy. CONCLUSIONS: This report suggests a potential utility of trastuzumab-based chemotherapy for HER2-positive CXPA.

[916]

**TÍTULO / TITLE:** - Fucoidan induces G1 phase arrest and apoptosis through caspases-dependent pathway and ROS induction in human breast cancer MCF-7 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Huazhong Univ Sci Technolog Med Sci. 2013 Oct;33(5):717-24. doi: 10.1007/s11596-013-1186-8. Epub 2013 Oct 20.

●● Enlace al texto completo (gratis o de pago) [1007/s11596-013-1186-8](#)

**AUTORES / AUTHORS:** - Banafa AM; Roshan S; Liu YY; Chen HJ; Chen MJ; Yang GX; He GY

**INSTITUCIÓN / INSTITUTION:** - The Genetic Engineering International Cooperation Base of Ministry of Science and Technology, Key Laboratory of Molecular Biophysics

of Ministry of Education, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, 430074, China, [amalbanafa@yahoo.com](mailto:amalbanafa@yahoo.com).

**RESUMEN / SUMMARY:** - Fucoidan is an active component of seaweed, which inhibits proliferation and induces apoptosis of several tumor cells while the detailed mechanisms underlying this process are still not clear. In this study, the effect of Fucoidan on the proliferation and apoptosis of human breast cancer MCF-7 cells and the molecular mechanism of Fucoidan action were investigated. Viable cell number of MCF-7 cells was decreased by Fucoidan treatment in a dose-dependent manner as measured by MTT assay. Fucoidan treatment resulted in G1 phase arrest of MCF-7 cells as revealed by flow cytometry, which was associated with the decrease in the gene expression of cyclin D1 and CDK-4. Annexin V/PI staining results showed that the number of apoptotic cells was associated with regulation of cytochrome C, caspase-8, Bax and Bcl-2 at transcriptional and translational levels. Both morphologic observation and Hoechst 33258 assay results confirmed the pro-apoptotic effect of Fucoidan. Meanwhile, the ROS production was also increased by Fucoidan treatment, which suggested that Fucoidan induced oxidative damage in MCF-7 cells. The results of present study demonstrated that Fucoidan could induce G1 phase arrest and apoptosis in MCF-7 cells through regulating the cell cycle and apoptosis-related genes or proteins expression, and ROS generation is also involved in these processes.

[917]

**TÍTULO / TITLE:** - Novel Association Between CD74 Polymorphisms and Hematologic Toxicity in Patients With NSCLC After Platinum-Based Chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lung Cancer. 2013 Nov 9. pii: S1525-7304(13)00183-6. doi: 10.1016/j.clcc.2013.08.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.clcc.2013.08.006](http://1016/j.clcc.2013.08.006)

**AUTORES / AUTHORS:** - Tan X; Wu Q; Cai Y; Zhao X; Wang S; Gao Z; Yang Y; Li X; Qian J; Wang J; Su B; Chen H; Han B; Jiang G; Lu D

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Disease, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Platinum-based chemotherapy regimens can cause DNA damage. Macrophage migration inhibitory factor (MIF) plays an important role in the regulation of the cell cycle by either controlling the activity of the SKP1-Cullin/Cdc53-F-box protein ubiquitin ligase (SCF) complex or activating its receptor, CD74. PATIENTS AND METHODS: We used a pathway-based approach to investigate the association between genetic polymorphisms in MIF-pathway genes and the outcomes of platinum-based chemotherapy in advanced non-small-cell lung cancer (NSCLC). We used iSelect 24x1 HD BeadChip (Illumina, Inc, San Diego, CA) to genotype 32 tag and potentially functional single nucleotide polymorphisms (SNPs) of 8 selected genes and evaluated their associations with different outcomes for 1004 patients with advanced NSCLC treated with platinum-based chemotherapy. In particular, gastrointestinal toxicity and hematologic toxicity were analyzed for associations with specific genotypes, alleles, and haplotypes. RESULTS: Two polymorphisms of CD74, rs2748249 (C/A) and rs1560661 (A/G), were significantly associated with hematologic toxicity. Carrying an A allele in rs2748249 was associated with higher hematologic toxicity (odds ratio [OR], 1.72; 95% confidence interval [CI],

1.24-2.39; P = .001) and carrying a G allele in rs1560661 was associated with lower hematologic toxicity (OR, 0.42; 95% CI, 0.25-0.70; P = .00099) compared with the wild type. Haplotype analysis revealed that the patients with the CG haplotype (consisting of rs2748249 and rs1560661) had reduced hematologic toxicity compared with patients with other haplotypes (OR, 0.70; 95% CI, 0.56-0.87; P = .0013). The binding domain shared by 3 transcription factors (activator protein-2alpha [AP-2alpha], progesterone response A/B, and TFII-I) comprised the 2 SNPs that may be involved in the regulation of CD74-related B-cell survival. CONCLUSION: Our study is the first to suggest, to our knowledge, that polymorphisms in CD74 might be a marker of lower hematologic toxicity for patients with advanced NSCLC receiving platinum-based chemotherapy.

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[918]

**TÍTULO / TITLE:** - Combination of the PI3K Inhibitor ZSTK474 with a PSMA-Targeted Immunotoxin Accelerates Apoptosis and Regression of Prostate Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Neoplasia. 2013 Oct;15(10):1172-83.

**AUTORES / AUTHORS:** - Baiz D; Hassan S; Choi YA; Flores A; Karpova Y; Yancey D; Pullikuth A; Sui G; Sadelain M; Debinski W; Kulik G

**INSTITUCIÓN / INSTITUTION:** - Department of Cancer Biology and Comprehensive Cancer Center, Wake Forest School of Medicine, Winston-Salem, NC.

**RESUMEN / SUMMARY:** - The phosphoinositide 3-kinase (PI3K) pathway is activated in most advanced prostate cancers, yet so far treatments with PI3K inhibitors have been at best tumorostatic in preclinical cancer models and do not show significant antitumor efficacy in clinical trials. Results from tissue culture experiments in prostate cancer cells suggest that PI3K inhibitors should be combined with other cytotoxic agents; however, the general toxicity of such combinations prevents translating these experimental data into preclinical and clinical models. We investigated the emerging concept of tumor-targeted synthetic lethality in prostate cancer cells by using the pan-PI3K inhibitor ZSTK474 and the immunotoxin J591PE, a protein chimera between the single-chain variable fragment of the monoclonal antibody J591 against the prostate-specific membrane antigen (PSMA) and the truncated form of the Pseudomonas aeruginosa exotoxin A (PE38QQR). The combination of ZSTK474 and J591PE increased apoptosis within 6 hours and cell death (monitored at 24-48 hours) in the PSMA-expressing cells LNCaP, C4-2, and C4-2Luc but not in control cells that do not express PSMA (PC3 and BT549 cells). Mechanistic analysis suggested that induction of apoptosis requires Bcl-2-associated death promoter (BAD) dephosphorylation and decreased expression of myeloid leukemia cell differentiation protein 1 (MCL-1). A single injection of ZSTK474 and J591PE into engrafted prostate cancer C4-2Luc cells led to consistent and stable reduction of luminescence within 6 days. These results suggest that the combination of a PI3K inhibitor and a PSMA-targeted protein synthesis inhibitor toxin represents a promising novel strategy for advanced prostate cancer therapy that should be further investigated.

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[919]

**TÍTULO / TITLE:** - Elevated C-reactive protein values predict nodal metastasis in patients with penile cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Urol. 2013 Oct 22;13(1):53.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2490-13-53](https://doi.org/10.1186/1471-2490-13-53)

**AUTORES / AUTHORS:** - Al Ghazal A; Steffens S; Steinestel J; Lehmann R; Schnoeller TJ; Schulte-Hostede A; Wegener G; Jentzmik F; Schrader M; Kuczyk MA; Schrader AJ

**RESUMEN / SUMMARY:** - BACKGROUND: The nodal status is a strong predictor for cancer specific death in patients with penile carcinoma, and the C-reactive protein (CRP) level at diagnosis has recently been shown to be associated with poor clinical outcome in various solid malignancies. Therefore, this retrospective study was performed to evaluate the association between preoperative CRP levels and the incidence of nodal metastasis in patients with squamous cell carcinoma (SCC) of the penis. METHODS: The analysis included 51 penile cancer patients who underwent either radical or partial penectomy for pT1-4 penile cancer between 1990 and 2010. The nodal status was correlated with patient and tumor specific characteristics. RESULTS: Sixteen (31%) patients had lymph node metastasis at the time of penile cancer surgery. Nodal status was associated with tumor stage but did not correlate significantly with tumor grade. In contrast, high presurgical CRP levels were significantly associated with the diagnosis of nodal involvement ( $p = 0.04$ ). The optimal CRP cut-off value to predict lymph node metastasis was set at 20 mg/l based on ROC analysis. CONCLUSIONS: Since a high preoperative serum CRP level was closely correlated with nodal disease, it could be used as an additional marker to help identify patients with penile cancer who may benefit from inguinal lymph node dissection.

[920]

**TÍTULO / TITLE:** - Prognostic Value of a Nine-Gene Signature in Glioma Patients Based on mRNA Expression Profiling.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - CNS Neurosci Ther. 2013 Nov 27. doi: 10.1111/cns.12171.

●● Enlace al texto completo (gratis o de pago) [1111/cns.12171](https://doi.org/10.1111/cns.12171)

**AUTORES / AUTHORS:** - Bao ZS; Li MY; Wang JY; Zhang CB; Wang HJ; Yan W; Liu YW; Zhang W; Chen L; Tao J

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

**RESUMEN / SUMMARY:** - INTRODUCTION: Gliomas are the most common primary brain tumors in adults and a significant cause of cancer-related mortality. A 9-gene signature was identified as a novel prognostic model reflecting survival situation obviously in gliomas. AIMS: To identify an mRNA expression signature to improve outcome prediction for patients with different glioma grades. RESULTS: We used whole-genome mRNA expression microarray data of 220 glioma samples of all grades from the Chinese Glioma Genome Atlas (CGGA) database (<http://www.cgga.org.cn>) as a discovery set and data from Rembrandt and GSE16011 for validation sets. Data from every single grade were analyzed by the Kaplan-Meier method with a two-sided log-rank test. Univariate Cox regression and linear risk score formula were applied to derive a gene signature with better prognostic performance. We found that patients who had high risk score according to the signature had poor overall survival compared with patients who had low risk score. Highly expressed genes in the high-risk group were analyzed by gene ontology (GO) and gene set variation analysis (GSVA). As a result, the reason for the divisibility of gliomas was likely due to cell life processes and adhesion. CONCLUSION: This 9-gene-signature prediction model provided a more

accurate predictor of prognosis that denoted patients with high risk score have poor outcome. Moreover, these risk models based on defined molecular profiles showed the considerable prospect in personalized cancer management.

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[921]

**TÍTULO / TITLE:** - Concurrent radiotherapy plus epidermal growth factor receptor inhibitors in patients with human papillomavirus-related head and neck cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Nov 6.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1099-9](#)

**AUTORES / AUTHORS:** - Pajares B; Perez-Villa L; Trigo JM; Toledo MD; Alvarez M; Jimenez B; Medina JA; de Luque V; Jerez JM; Alba E

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Servicio de Oncología Medica del Hospital Clinico Virgen de la Victoria, Campus Teatinos s/n, 29010, Malaga, España, [bella.pajares@fundacionimabis.org](mailto:bella.pajares@fundacionimabis.org).

**RESUMEN / SUMMARY:** - PURPOSE: Concurrent radio-chemotherapy (RT-CT) is the standard treatment for locally advanced head and neck squamous cell carcinoma (LA-HNSCC), but RT plus epidermal growth factor receptor (EGFR) inhibitors is an effective option when CT is not appropriate. Human papillomavirus (HPV) is associated with an improved prognosis in LA-HNSCC; however, it has not been fully studied as a prognostic factor after RT + EGFR inhibitors. EXPERIMENTAL DESIGN: Immunohistochemical expression of p16INK4A and PCR of HPV16 DNA were retrospectively analyzed in tumor blocks from 52 stage III/IV LA-HNSCC patients treated with RT + EGFR inhibitors. Disease-free survival (DFS) and overall survival (OS) were analyzed by the Kaplan-Meier method. RESULTS: DNA of HPV16 was found in six of 52 tumors (12 %) and p16 positivity in eight tumors (15 %). After a median follow-up time of 45 months (6-110), p16-positive patients treated with RT + EGFR inhibitors showed an improved DFS (2-year DFS 75 vs. 44 %, HR 0.25, 95 % CI 0.06-0.99, p = 0.047) compared with p16-negative patients. These differences were outperformed when compared by HPV16 status (2-year OS rates of 83 vs. 58 %, HR 0.17, 95 % CI 0.02-0.99, p = 0.049 and 2-year DFS rates of 83 vs. 45 %, HR 0.17, 95 % CI 0.02-0.99, p = 0.049). In the Cox regression analysis with OS as the end point, ECOG 0-1 was the only prognostic factor independently associated with a good prognosis in the multivariable analysis. CONCLUSION: In this study, p16/HPV16-positive patients with LA-HNSCC treated with RT + EGFR inhibitors showed a better survival, not confirmed in multivariate analysis.

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[922]

**TÍTULO / TITLE:** - Role of Ki67 in predicting resistance to adjuvant tamoxifen in postmenopausal breast cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Egypt Natl Canc Inst. 2013 Dec;25(4):181-91. doi: 10.1016/j.jnci.2013.02.001. Epub 2013 Apr 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.jnci.2013.02.001](#)

**AUTORES / AUTHORS:** - Elzawahry HM; Saber MM; Mokhtar NM; Zeeneldin AA; Ismail YM; Alieldin NH

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology/Hematology, National Cancer Institute, Cairo University, Egypt.

**RESUMEN / SUMMARY:** - INTRODUCTION: Breast cancer (BC) is a major health problem in Egypt and worldwide. Its prognosis depends not only on tumor stage but also on tumor biology. AIM: To correlate the expression of Ki67 with the clinical outcomes of early hormone-receptor positive postmenopausal BC patients who are receiving tamoxifen. METHODS: This cohort study included 70 patients. They were followed up for a minimum of 2years. Ki67 was assessed on paraffin-embedded blocks using immunohistochemistry methods. RESULTS: The median Ki67 value was 22.5% (IQR, 10%-50%). Ki67 was significantly higher in patients with HER2 positive tumors compared to HER2 negative tumors. After a median follow up period of 53months, 22 patients (31%) developed disease recurrence either loco-regional or distant in 5.7% and 30%, respectively. Recurrent patients had significantly higher tumor stage, nodal stage and Ki67 values compared to non-recurrent cases. The 2-, 3- and 5-year overall survival (OS) and disease-free survival (DFS) rates were 100% & 91%, 98% & 84% and 77% & 59%, respectively. DFS was significantly worse with higher TNM stage, lower ER expression and higher Ki67 values. OS was significantly worse in patients with Ki67 values 30%. Ki67 30% was an independent predictor of recurrence, poor DFS and OS. CONCLUSION: High Ki67 expression is predictive of poor prognosis and of resistance to adjuvant tamoxifen therapy in postmenopausal BC. We recommend considering Ki67 as one of the risk factors that guide adjuvant treatment decisions.

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[923]

**TÍTULO / TITLE:** - miR-30b and miR-30c expression predicted response to tyrosine kinase inhibitors as first line treatment in non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin Med J (Engl). 2013 Dec;126(23):4435-9.

**AUTORES / AUTHORS:** - Gu YF; Zhang H; Su D; Mo ML; Song P; Zhang F; Zhang SC

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Beijing Tuberculosis and Thoracic Tumor Research Institute/Beijing Chest Hospital, Capital Medical University, Beijing 101149, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Aberrantly expressed microRNAs are a hallmark of cancer, and microRNA expression profiling is associated with tumor progression and response to chemotherapy, suggesting their potential application as prognostic and predictive biomarkers. The role of microRNAs in lung cancer remains elusive. It has been recently reported that epidermal growth factor receptor (EGFR) and hepatocyte growth factor receptor (MET) tyrosine kinase can regulate expression of specific microRNAs including miR-30b, miR-30c, miR-221, miR-222, miR-103 and miR-203, and induce tumorigenesis and gefitinib resistance in lung cancers. We intend to study the role of miR-30b and miR-30c expression in predicting response to tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). METHODS: We have therefore retrospectively examined expression of miR-30b miR-30c in 41 formalin fixed paraffin embedded tissue samples from NSCLC patients when TKIs were used as first line therapy. RESULTS: We found a significant correlation between expression of miR-30b and miR-30c. Furthermore, miR-30b and miR-30c expression correlated with short-term response. Kaplan-Meier analysis further revealed that the expression of miR-30b and miR-30c predicted progression free survival and the overall survival rate in the examined cohort. CONCLUSION: Our study identified miR-30b and miR-30c as useful prognostic predictors in NSCLC patients who underwent first line treatment with TKIs.

[924]

**TÍTULO / TITLE:** - Clinical significance of L-type amino acid transporter 1 expression as a prognostic marker and potential of new targeting therapy in biliary tract cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Oct 16;13(1):482.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-482](#)

**AUTORES / AUTHORS:** - Kaira K; Sunose Y; Ohshima Y; Ishioka NS; Arakawa K; Ogawa T; Sunaga N; Shimizu K; Tominaga H; Oriuchi N; Itoh H; Nagamori S; Kanai Y; Yamaguchi A; Segawa A; Ide M; Mori M; Oyama T; Takeyoshi I

**RESUMEN / SUMMARY:** - BACKGROUND: The expression of L-type amino acid transporter 1 (LAT1) has been described to play essential roles in tumor cell growth and survival. However, it remains unclear about the clinicopathological significance of LAT1 expression in biliary tract cancer. This study was conducted to determine biological significance of LAT1 expression and investigate whether LAT1 could be a prognostic biomarker for biliary tract cancer. METHODS: A total of 139 consecutive patients with resected pathologic stage I-IV biliary tract adenocarcinoma were retrospectively reviewed. Tumor specimens were stained by immunohistochemistry for LAT1, Ki-67, microvessel density determined by CD34, and p53; and prognosis of patients was correlated. Biological significance of LAT1 expression was investigated by in vitro and in vivo experiments with LAT inhibitor, 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH) using cholangiocarcinoma cell line. RESULTS: In total patients, high LAT1 expressions were recognized in 64.0%. The expression of LAT1 was closely correlated with lymphatic metastases, cell proliferation and angiogenesis, and was a significant indicator for predicting poor outcome after surgery. LAT1 expression was a significant independent predictor by multivariate analysis. Both in vitro and in vivo preliminary experiments indicated that BCH significantly suppressed growth of the tumor and yielded an additive therapeutic efficacy to gemcitabine and 5-FU. CONCLUSIONS: High expression of LAT1 is a promising pathological marker to predict the outcome in patients with biliary tract adenocarcinoma. Inhibition of LAT1 may be an effective targeted therapy for this distressing disease.

[925]

**TÍTULO / TITLE:** - Proteomic analysis of differentially expressed proteins in 5-fluorouracil-treated human breast cancer MCF-7 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Nov 12.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1127-9](#)

**AUTORES / AUTHORS:** - Cai J; Chen S; Zhang W; Wei Y; Lu J; Xing J; Dong Y

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacy, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an, 710061, China.

**RESUMEN / SUMMARY:** - BACKGROUND: 5-Fluorouracil (5-Fu) is a commonly used chemotherapeutic agent in clinical care of breast cancer patients. However, the mechanism of how the 5-Fu works is complex and still largely unknown. OBJECTIVE: The objective of this study was to understand the mechanism further and explore the new targets of 5-Fu. METHODS: The differentially expressed proteins induced by 5-Fu in human breast cancer MCF-7 cells were identified by proteomic analysis. Four

differentially expressed proteins were validated using Western blot and quantitative real-time reverse-transcription polymerase chain reaction analysis for protein and mRNA levels. The effect of 5-Fu on MCF-7 cells was determined by cell viability assay, transmission electron microscopy and flow cytometry analysis. RESULTS: 5-Fu dose-dependently inhibited cell proliferation with the IC50 value of 98.2  $\mu$ M. 5-Fu also induced obviously morphological change and apoptosis in MCF-7 cells. Twelve differentially expressed proteins involved in energy metabolism, cytoskeleton, cellular signal transduction and tumor invasion and metastasis were identified. CONCLUSION: These results may provide a new insight into the molecular mechanism of 5-Fu in therapy of breast cancer.

[926]

**TÍTULO / TITLE:** - SLCO1B1 and SLC19A1 Gene Variants and Irinotecan-Induced Rapid Response and Survival: A Prospective Multicenter Pharmacogenetics Study of Metastatic Colorectal Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 15;8(10):e77223. doi: 10.1371/journal.pone.0077223.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0077223](#)

**AUTORES / AUTHORS:** - Huang L; Zhang T; Xie C; Liao X; Yu Q; Feng J; Ma H; Dai J; Li M; Chen J; Zang A; Wang Q; Ge S; Qin K; Cai J; Yuan X

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P. R. China.

**RESUMEN / SUMMARY:** - BACKGROUND: Rapid response to chemotherapy in metastatic colorectal cancer (mCRC) patients (response within 12 weeks of chemotherapy) may increase the chance of complete resection and improved survival. Few molecular markers predict irinotecan-induced rapid response and survival. Single-nucleotide polymorphisms (SNPs) in solute carrier genes are reported to correlate with the variable pharmacokinetics of irinotecan and folate in cancer patients. This study aims to evaluate the predictive role of 3 SNPs in mCRC patients treated with irinotecan and fluoropyrimidine-containing regimens. MATERIALS AND METHODS: Three SNPs were selected and genotyped in 137 mCRC patients from a Chinese prospective multicenter trial (NCT01282658). The chi-squared test, univariate and multivariable logistic regression model, and receiver operating characteristic analysis were used to evaluate correlations between the genotypes and rapid response. Kaplan-Meier survival analysis and Cox proportional hazard models were used to evaluate the associations between genotypes and survival outcomes. Benjamini and Hochberg False Discovery Rate correction was used in multiple testing. RESULTS: Genotype GA/AA of SNP rs2306283 of the gene SLCO1B1 and genotype GG of SNP rs1051266 of the gene SLC19A1 were associated with a higher rapid response rate (odds ratio [OR] =3.583 and 3.521, 95%CI =1.301-9.871 and 1.271-9.804, p=0.011 and p=0.013, respectively). The response rate was 70% in patients with both genotypes, compared with only 19.7% in the remaining patients (OR = 9.489, 95%CI = 2.191-41.093, Fisher's exact test p=0.002). Their significances were all maintained even after multiple testing (all p < 0.05). The rs2306283 GA/AA genotype was also an independent prognostic factor of longer progression-free survival (PFS) (hazard ratio = 0.402, 95%CI = 0.171-0.945, p=0.037). None of the SNPs predicted overall survival.

CONCLUSIONS: Polymorphisms of solute carriers' may be useful to predict rapid response to irinotecan plus fluoropyrimidine and PFS in mCRC patients. TRIAL

REGISTRY: ClinicalTrials.gov NCT01282658

<http://www.clinicaltrials.gov/ct2/show/NCT01282658>.

[927]

**TÍTULO / TITLE:** - Type 1 plasminogen activator inhibitor as a common risk factor for cancer and ischaemic vascular disease: the EPICOR study.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - British Medical J (BMJ). Acceso gratuito al texto completo.

●● Enlace a la Editora de la Revista <http://bmj.com/search.dtl>

●● Cita: British Medical J. (BMJ): <> Open. 2013 Nov 14;3(11):e003725. doi: 10.1136/bmjopen-2013-003725.

●● Enlace al texto completo (gratuito o de pago) [1136/bmjopen-2013-003725](http://1136/bmjopen-2013-003725)

**AUTORES / AUTHORS:** - Iacoviello L; Agnoli C; De Curtis A; di Castelnuovo A; Giurdanella MC; Krogh V; Mattiello A; Matullo G; Sacerdote C; Tumino R; Vineis P; de Gaetano G; Panico S; Donati MB

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Molecular and Nutritional Epidemiology, Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy.

**RESUMEN / SUMMARY:** - OBJECTIVES: We examined the association of plasminogen activator inhibitor-1 (PAI-1) levels with colorectal cancer, breast cancer, acute coronary syndrome (ACS) and ischaemic stroke. DESIGN: Nested case-cohort study. SETTING: The European Prospective Investigation into Cancer and Nutrition-Italy cohort. PARTICIPANTS: A centre-stratified random sample of 850 participants (286 men, 564 women) was selected as subcohort and compared with 303 colorectal cancers, 617 breast cancers, 688 ACS and 158 ischaemic strokes, in a mean follow-up of 9.11 years. MAIN OUTCOMES AND MEASURES: Primary incident cases of colon cancer, breast cancer, ACS and ischaemic stroke. PAI-1 levels were measured in citrated plasma by ELISA. HR and 95% CI, adjusted by relevant confounders and stratified by centre, were estimated by a Cox regression model using Prentice method. RESULTS: Individuals in the highest compared with the lowest quartile of PAI-1 had significantly increased risk of colorectal cancer (RR=2.28; 95% CI 1.46 to 3.55; P for trend<0.0012), breast cancer (HR=1.70; 95% CI 1.21 to 2.39; p<0.0055), ACS (HR=2.57; 95% CI 1.75 to 3.77; p<0.001) and ischaemic stroke (HR=2.27; 95% CI 1.28 to 4.03; p<0.0017), after adjustment for sex and age. Additional adjustment for disease-specific confounders, insulin or other metabolic variables did not modify the associations. Risk of colon cancer was stronger for men and for whole and distal colon localisation. Risk for breast cancer was stronger in postmenopausal women. CONCLUSIONS: Our data provide the first evidence that elevated levels of PAI-1 are potential risk factors for colorectal and breast cancer and a common pathway for cancer and cardiovascular disease.

[928]

**TÍTULO / TITLE:** - Phase I drug-interaction study of effects of calcium and magnesium infusions on oxaliplatin pharmacokinetics and acute neurotoxicity in colorectal cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Oct 25;13(1):495.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-495](https://doi.org/10.1186/1471-2407-13-495)

**AUTORES / AUTHORS:** - Han CH; Khwaounjoo P; Kilfoyle DH; Hill A; McKeage MJ

**RESUMEN / SUMMARY:** - BACKGROUND: Calcium and magnesium (Ca/Mg) infusions have been suggested as an effective intervention for preventing oxaliplatin-induced neurotoxicity, but the effects of Ca/Mg infusions on oxaliplatin pharmacokinetics, motor nerve hyperexcitability and acute neurotoxicity symptoms are unclear. METHODS: In this double blind crossover study, colorectal cancer patients undergoing oxaliplatin-based chemotherapy were randomised to receive Ca/Mg (1g Ca Gluconate plus 1g MgSO<sub>4</sub>) on cycle 1 and placebo (vehicle alone) on cycle 2, or to receive the same treatments in the opposite sequence. Study endpoints included plasma pharmacokinetics of intact oxaliplatin and free platinum; electromyography (EMG) detection of abnormal spontaneous high-frequency motor unit action potential discharges; and patient-reported acute neurotoxicity symptoms and their preferred study treatment for reducing these symptoms. RESULTS: Nineteen of 20 enrolled patients completed the study. Plasma pharmacokinetics of intact oxaliplatin and free platinum were similar when oxaliplatin was given with Ca/Mg or placebo (ratio of geometric means of AUC<sub>0-t</sub> with Ca/Mg or placebo: intact oxaliplatin, 0.95 (90% CI, 0.90 -- 1.01); free platinum, 0.99 (90% CI, 0.94 -- 1.05)). EMG motor nerve hyperexcitability scores were similar with Ca/Mg and placebo (mean difference in EMG score between Ca/Mg and placebo: -0.3 (95% CI, -2.2 -- 1.6)). Patient-reported acute neurotoxicity symptoms were similar in frequency with Ca/Mg and placebo. For reducing neurotoxic symptoms, fewer patients preferred Ca/Mg than placebo or neither treatment (26% versus 74%; P<0.01). CONCLUSIONS: Ca/Mg infusions do not alter the clinical pharmacokinetics of oxaliplatin and do not seem to reduce its acute neurotoxicity. Trial registration: Trial registration identifier ACTRN12611000738921.

[929]

**TÍTULO / TITLE:** - The Prognostic Significance of Elevated Levels of Serum Ferritin Before Chemotherapy in Patients With Non-Hodgkin Lymphoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lymphoma Myeloma Leuk. 2013 Oct 1. pii: S2152-2650(13)00429-1. doi: 10.1016/j.clml.2013.09.008.

●● Enlace al texto completo (gratis o de pago) [1016/j.clml.2013.09.008](https://doi.org/10.1016/j.clml.2013.09.008)

**AUTORES / AUTHORS:** - Yoh KA; Lee HS; Park LC; Lee EM; Shin SH; Park DJ; Ye BJ; Kim YS

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea.

**RESUMEN / SUMMARY:** - BACKGROUND: Elevated levels of serum ferritin have been documented to be an adverse prognostic factor in patients with hematologic malignancies undergoing hematopoietic stem cell transplantation. The purpose of this study was to estimate the correlation between elevated levels of serum ferritin and survival outcomes in patients with non-Hodgkin lymphoma (NHL). PATIENTS AND METHODS: A total of 267 patients who were newly diagnosed with NHL and who received chemotherapy between September 1999 and April 2012 were retrospectively analyzed. RESULTS: In multivariate analysis, other chemotherapy regimens excluding CHOP-like chemotherapy regimens (cyclophosphamide, adriamycin, vincristine, prednisolone) and RCHOP (rituximab plus CHOP), a high level of beta2-microglobulin,

a high-intermediate/high risk according to the international prognostic index (IPI), and elevated levels of serum ferritin were all significant independent prognostic factors for 5-year progression-free survival rates. RCHOP and other chemotherapy regimens, a high level of beta2-microglobulin, a high-intermediate/high IPI risk, and high levels of serum ferritin were significant independent prognostic factors for 5-year overall survival rates. CONCLUSION: Elevated levels of serum ferritin of 500 ng/mL or more as well as the use of chemotherapy regimens besides CHOP-like or RCHOP, a high-intermediate/high risk IPI, and a high level of beta2-microglobulin in NHL may be an important marker for predicting poor survival outcomes.

[930]

**TÍTULO / TITLE:** - Prognostic analysis of adjuvant chemotherapy in patients with nasopharyngeal carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 Oct;9(10):1469-76. doi: 10.2217/fon.13.100.

●● Enlace al texto completo (gratis o de pago) [2217/fon.13.100](#)

**AUTORES / AUTHORS:** - Lin CC; Chen TT; Lin CY; Hsieh CY; Lin PH; Chien CR; Chiu CF; Yeh SP

**INSTITUCIÓN / INSTITUTION:** - Division of Hematology & Oncology, Department of Internal Medicine, China Medical University Hospital, 2 Yude Road, Taichung, Taiwan, Republic of China.

**RESUMEN / SUMMARY:** - BACKGROUND: Concurrent chemoradiation has become the standard of treatment in locally advanced nasopharyngeal carcinoma. However, the exact magnitude of the benefits of adjuvant chemotherapy is still unclear. MATERIALS & METHODS: This is a retrospective assessment of 181 patients with newly diagnosed, locally advanced nasopharyngeal carcinoma who received concurrent chemoradiation followed by adjuvant chemotherapy with cisplatin plus fluorouracil in one institution between 2004 and 2010. RESULTS: The median follow-up period was 40 months (range: 2.1-96.6 months). The estimated 5-year survival rate of patients with and without adjuvant chemotherapy were 83.6 and 66.7%, respectively ( $p = 0.027$ ). Patients receiving two to three cycles of adjuvant chemotherapy had improved outcomes compared with those without adjuvant chemotherapy or who had received one cycle. Multivariate analysis showed that both advanced stage and suboptimal treatment of adjuvant chemotherapy were adverse risk factors in terms of overall survival and disease-specific survival. CONCLUSION: Adjuvant chemotherapy with two to three cycles of cisplatin plus fluorouracil improved the survival of nasopharyngeal carcinoma patients.

[931]

**TÍTULO / TITLE:** - RKIP phosphorylation and STAT3 activation is inhibited by oxaliplatin and camptothecin and are associated with poor prognosis in stage II colon cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Oct 8;13:463. doi: 10.1186/1471-2407-13-463.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-463](#)

**AUTORES / AUTHORS:** - Cross-Knorr S; Lu S; Perez K; Guevara S; Brilliant K; Pisano C; Quesenberry PJ; Resnick MB; Chatterjee D

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Rhode Island Hospital and The Alpert Medical School of Brown University, Providence, RI 02903, USA.

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**RESUMEN / SUMMARY:** - BACKGROUND: A major obstacle in treating colorectal cancer (CRC) is the acquired resistance to chemotherapeutic agents. An important protein in the regulation of cancer cell death and clinical outcome is Raf kinase inhibitor protein (RKIP). In contrast, activated signal transducer and activator of transcription 3 (STAT3) is a protein that promotes tumor cell survival by inhibiting apoptosis and has an important role in cancer progression in many of cancer types. The aim of this study was to evaluate the regulation of RKIP and STAT3 after treatment with clinically relevant chemotherapeutic agents (camptothecin (CPT) and oxaliplatin (OXP)) and the cytokine interleukin-6 (IL-6) in HCT116 colon cancer cells as well as evaluate the association between RKIP and STAT3 with clinical outcome of Stage II colon cancer patients. METHODS: HCT-116 colon cancer cells were treated with CPT, OXP, and IL-6 separately or in combination in a time and dose-dependent manner and examined for phosphorylated and non-phosphorylated RKIP and STAT3 via Western blot analysis. STAT3 transcriptional activity was measured via a luciferase reporter assay in HCT116 cells treated with CPT, IL-6 or transfected with JAK 1, 2 separately or in combination. We extended these observations and determined STAT3 and RKIP/pRKIP in tumor microarrays (TMA) in stage II colon cancer patients. RESULTS: We demonstrate IL-6-mediated activation of STAT3 occurs in conjunction with the phosphorylation of RKIP in vitro in human colon cancer cells. OXP and CPT block IL-6 mediated STAT3 activation and RKIP phosphorylation via the inhibition of the interaction of STAT3 with gp130. We determined that STAT3 and nuclear pRKIP are significantly associated with poor patient prognosis in stage II colon cancer patients. CONCLUSIONS: In the analysis of tumor samples from stage II colon cancer patients and the human colon carcinoma cell line HCT116, pRKIP and STAT3, 2 proteins potentially involved in the resistance to conventional treatments were detected. The phosphorylation of pRKIP and STAT3 are induced by the cytokine IL-6 and suppressed by the chemotherapeutic drugs CPT and OXP. Therefore, these results suggest that STAT3 and pRKIP may serve as prognostic biomarkers in stage II colon cancer patients and may improve chemotherapy.

[932]

**TÍTULO / TITLE:** - Demethylating agent decitabine induces autologous cancer testis antigen specific cytotoxic T lymphocytes in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin Med J (Engl). 2013 Dec;126(23):4552-6.

**AUTORES / AUTHORS:** - Zhou JH; Yao YS; Wang LX; Wang J; Li YH; Jiang MM; Zhou MH; Gao XN; Li RS; Wang LL; Yu L

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology, Chinese People's Liberation Army General Hospital, Beijing 100853, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Cancer testis antigens (CTAs) are a novel group of tumor associated antigens. Demethylating agent decitabine was reported to be able to up-regulate CTAs through its hypomethylation mechanism, thus enhance the immunogenicity of leukemia cells. However, few researches have ever focused on the

questions that whether this immunostimulatory effect of decitabine could induce autologous CTA specific cytotoxic T lymphocytes (CTLs) in vivo, and if so, whether this effect contributes to disease control. In this study, we aimed to show that decitabine could induce specific autologous CTLs against some mouse CTAs in leukemia cells in vitro and in vivo. METHODS: Several mouse CTAs were screened by RT-PCR. CTL specific to one of the CTAs named P1A was detected and sorted by P1A specific dimer by flow cytometry. The activity of specific CTLs was measured by real time RT-PCR. RESULTS: We firstly screened expression of some CTAs in mouse leukemia cells before and after decitabine treatment and found that decitabine treatment did up-regulate expression of many CTAs. Then we measured the CTLs' activity specific to a mouse CTA P1A in vivo and showed that this activity increased after decitabine treatment. Finally, we sorted these in vivo induced P1A specific CTLs by flow cytometry and demonstrated their cytotoxicity against decitabine treated leukemia cells. CONCLUSIONS: Our study showed the autologous immune response induced by decitabine in vivo. And more importantly, we firstly proved that this response may contribute to disease control. We believe that this immunostimulatory effect is another anti-cancer mechanism of decitabine, and this special effect would inspire new applications of decitabine in the field of leukemia treatment in the future.

[933]

**TÍTULO / TITLE:** - Protein Kinase CK2 Inhibition Down Modulates the NF-kappaB and STAT3 Survival Pathways, Enhances the Cellular Proteotoxic Stress and Synergistically Boosts the Cytotoxic Effect of Bortezomib on Multiple Myeloma and Mantle Cell Lymphoma Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Sep 27;8(9):e75280. doi: 10.1371/journal.pone.0075280.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0075280](#)

**AUTORES / AUTHORS:** - Manni S; Brancalion A; Mandato E; Tubi LQ; Colpo A; Pizzi M; Cappellesso R; Zaffino F; Di Maggio SA; Cabrelle A; Marino F; Zambello R; Trentin L; Adami F; Gurrieri C; Semenzato G; Piazza F

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Hematology and Clinical Immunology Branch, University of Padova, Padova, Italy ; Myeloma and Lymphoma Pathobiology Laboratory, Hematologic Malignancies Unit, Venetian Institute of Molecular Medicine, Padova, Italy.

**RESUMEN / SUMMARY:** - CK2 is a pivotal pro-survival protein kinase in multiple myeloma that may likely impinge on bortezomib-regulated cellular pathways. In the present study, we investigated CK2 expression in multiple myeloma and mantle cell lymphoma, two bortezomib-responsive B cell tumors, as well as its involvement in bortezomib-induced cytotoxicity and signaling cascades potentially mediating bortezomib resistance. In both tumors, CK2 expression correlated with that of its activated targets NF-kappaB and STAT3 transcription factors. Bortezomib-induced proliferation arrest and apoptosis were significantly amplified by the simultaneous inhibition of CK2 with two inhibitors (CX-4945 and K27) in multiple myeloma and mantle cell lymphoma cell lines, in a model of multiple myeloma bone marrow microenvironment and in cells isolated from patients. CK2 inhibition empowered bortezomib-triggered mitochondrial-dependent cell death. Phosphorylation of NF-

kappaB p65 on Ser529 (a CK2 target site) and rise of the levels of the endoplasmic reticulum stress kinase/endoribonuclease Ire1alpha were markedly reduced upon CK2 inhibition, as were STAT3 phospho Ser727 levels. On the contrary, CK2 inhibition increased phospho Ser51 eIF2alpha levels and enhanced the bortezomib-dependent accumulation of poly-ubiquitylated proteins and of the proteotoxic stress-associated chaperone Hsp70. Our data suggest that CK2 over expression in multiple myeloma and mantle cell lymphoma cells might sustain survival signaling cascades and can antagonize bortezomib-induced apoptosis at different levels. CK2 inhibitors could be useful in bortezomib-based combination therapies.

[934]

**TÍTULO / TITLE:** - Identification of new prognostic biomarkers for Stage III metastatic melanoma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncoimmunology. 2013 Sep 1;2(9):e25564. Epub 2013 Jul 3.

●● Enlace al texto completo (gratis o de pago) [4161/onci.25564](#)

**AUTORES / AUTHORS:** - Kakavand H; Scolyer RA; Thompson JF; Mann GJ

**INSTITUCIÓN / INSTITUTION:** - Melanoma Institute Australia; North Sydney, NSW Australia ; The University of Sydney; Sydney, NSW Australia.

**RESUMEN / SUMMARY:** - Accurately predicting disease outcome among patients bearing Stage III metastatic melanoma is complex. However, current advances in personalized medicine call for ever more precise prognostic assessments, as these have a significant impact not only on the design and analysis of clinical trials, but also on therapeutic decision-making.

[935]

**TÍTULO / TITLE:** - 20(S)-protopanaxadiol triggers mitochondrial-mediated apoptosis in human lung adenocarcinoma A549 cells via inhibiting the PI3K/Akt signaling pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Chin Med. 2013;41(5):1137-52. doi: 10.1142/S0192415X13500778.

●● Enlace al texto completo (gratis o de pago) [1142/S0192415X13500778](#)

**AUTORES / AUTHORS:** - Zhang YL; Zhang R; Xu HL; Yu XF; Qu SC; Sui DY

**INSTITUCIÓN / INSTITUTION:** - Department of Bioengineering, College of Chemistry, Chemical Engineering and Bioengineering, Donghua University, Shanghai 201620, China.

**RESUMEN / SUMMARY:** - 20(S)-Protopanaxadiol (PPD), an aglycone saponin ginsenoside isolated from *Panax quinquefolium* L, has been shown to inhibit the growth and proliferation in several cancer lines. However, the underlying molecular mechanisms remain poorly understood. In this study, we investigated the apoptosis-induced effects and the mechanism of 20(S)-PPD on human lung adenocarcinoma A549 cells. 20(S)-PPD showed a potent antiproliferative activity against A549 cells by triggering apoptosis. 20(S)-PPD-induced apoptosis was characterized by a dose-dependent loss of the mitochondrial membrane, release of cytochrome c, second mitochondria-derived activator of caspase (Smac) and apoptosis-inducing factor (AIF), activation of caspase-9/-3, and cleavage of poly (ADP-ribose) polymerase (PARP). Caspase-dependence was indicated by the ability of the pan-caspase inhibitor z-VAD-fmk to attenuate 20(S)-PPD-induced apoptosis. After treatment with 20(S)-PPD, the

proportion of A549 cells at the G0/G1 phase increased, while cells at the S and G2/M phases decreased. Furthermore, 20(S)-PPD also triggered down-regulation of phosphorylated Akt (Ser473/Thr308) and glycogen synthase kinase 3beta (GSK 3beta). Knockdown of GSK 3beta with siRNA promoted the apoptotic effects of 20(S)-PPD. These results revealed an unexpected mechanism of action for this unique ginsenoside: triggering a mitochondrial-mediated, caspase-dependent apoptosis via down-regulation of the PI3K/Akt signaling pathway in A549 cells. Our findings encourage further studies of 20(S)-PPD as a promising chemopreventive agent against lung cancer.

[936]

**TÍTULO / TITLE:** - Variable copy number of mitochondrial DNA (mtDNA) predicts worse prognosis in advanced gastric cancer patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Diagn Pathol. 2013 Oct 21;8(1):173.

●● Enlace al texto completo (gratis o de pago) [1186/1746-1596-8-173](#)

**AUTORES / AUTHORS:** - Zhang G; Qu Y; Dang S; Yang Q; Shi B; Hou P

**RESUMEN / SUMMARY:** - BACKGROUND: Change of mitochondrial DNA (mtDNA) copy number is widely reported in various human cancers, including gastric cancer, and is considered to be an important hallmark of cancers. However, there is remarkably little consensus on the value of variable mtDNA content in the prognostic evaluation of this cancer. METHODS: Using real-time quantitative PCR approach, we examined mtDNA copy number in a cohort of gastric cancers and normal gastric tissues, and explored the association of variable mtDNA content with clinical outcomes of gastric cancer patients. RESULTS: Our data showed that the majority of gastric cancer patients had low mtDNA content as compared to control subjects although the relative mean mtDNA content was higher in the former than the latter. Moreover, we found that variable mtDNA content was strongly associated with lymph node metastasis and cancer-related death of the patients with late-stage tumors. Notably, variable mtDNA content did not affect overall survival of gastric cancer patients, however, we found that increased mtDNA content was associated with poor survival in the patients with late-stage tumors. CONCLUSION: In this study, we demonstrated that variable mtDNA content markedly increased the risk of lymph node metastasis and high mortality of the patients with late-stage tumors. Additionally, we found a strong link between increased mtDNA content and worse survival of the patients with late-stage tumors. Taken together, variable mtDNA content may be a valuable poor prognostic factor for advanced gastric cancer patients. Virtual slides: The virtual slide(s) for this article can be found here:

<http://www.diagnosticpathology.dianomx.eu/vs/1344721463103353>.

[937]

**TÍTULO / TITLE:** - Gene aberrations of RRM1 and RRM2B and outcome of advanced breast cancer after treatment with docetaxel with or without gemcitabine.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Nov 12;13(1):541.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-541](#)

**AUTORES / AUTHORS:** - Jorgensen CL; Ejlersen B; Bjerre KD; Balslev E; Nielsen DL; Nielsen KV

**RESUMEN / SUMMARY:** - BACKGROUND: The purpose of the present study was to retrospectively evaluate whether copy number changes of the genes encoding the ribonucleotide reductase subunit M1 (RRM1) and/or subunit M2B (RRM2B) predict sensitivity to gemcitabine administered in combination with docetaxel compared to single agent docetaxel in advanced breast cancer patients. METHODS: Primary tumor samples from patients randomly assigned to gemcitabine plus docetaxel or docetaxel alone were analyzed for RRM1 and RRM2B copy number changes using Fluorescence In Situ Hybridization (FISH) technology with probes covering respectively RRM1 at 11p15.5 and a reference probe covering the centromere of chromosome 11 (CEN-11), and RRM2B at 8q22.3 and a reference probe covering the centromere of chromosome 8 (CEN-8). The assays were validated in a material of 60 normal breast samples. Time to progression (TTP) was the primary endpoint. Overall survival (OS) and response rate (RR) were secondary endpoints. Associations between RRM1/CEN-11 and/or RRM2B/CEN-8 ratios and time-to-event endpoints were analyzed by unadjusted and adjusted Cox proportional hazards regression models. Heterogeneity of treatment effects on TTP and OS according to gene status were investigated by subgroup analyses, and the Wald test was applied. All statistical tests were two-sided. RESULTS: FISH analysis for both RRM1 and RRM2B was successful in 251 patients. RRM1 and RRM2B aberrations (deletions and amplifications) were observed in 15.9% and 13.6% of patients, respectively. RRM1 aberrations were associated with a decreased OS in the time interval 1.5-7.4 years (hazard ratio = 1.72, 95% confidence interval = 1.05-2.79, P = 0.03). RRM2B aberrations alone or in combination with RRM1 aberrations had no prognostic impact in terms of TTP or OS. RR was not different by gene status. No significant differences were detected in TTP or OS within subgroups according to gene status and chemotherapy regimen. CONCLUSIONS: This study demonstrated the presence of RRM1 and RRM2B copy number changes in primary breast tumor specimens. Nevertheless, we found no support of the hypothesis that aberrations of RRM1 or RRM2B, neither individually nor in combination, are associated with an altered clinical outcome following chemotherapy with gemcitabine in combination with docetaxel compared to docetaxel alone in advanced breast cancer patients.

[938]

**TÍTULO / TITLE:** - Genetic variation in the serotonin transporter and HTR1B receptor predicts reduced bone formation during serotonin reuptake inhibitor treatment in older adults.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Biol Psychiatry. 2013 Sep 30.

●● Enlace al texto completo (gratis o de pago) [3109/15622975.2013.832380](#)

**AUTORES / AUTHORS:** - Garfield LD; Muller DJ; Kennedy JL; Mulsant BH; Reynolds CF 3rd; Teitelbaum SL; Civitelli R; Dixon D; Todorov AA; Lenze EJ

**INSTITUCIÓN / INSTITUTION:** - Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA.

**RESUMEN / SUMMARY:** - Objectives. Studies have reported an association between serotonin reuptake inhibitors (SRIs) and accelerated bone loss. Genetic variation in the serotonin system might modulate bone metabolism changes during SRI treatment. In a

clinical trial we examined functional genetic polymorphisms of serotonin transporter and receptors involved in bone metabolism to determine whether they predict changes in bone metabolism during SRI treatment. Methods. In 69 adults (age  $\geq 60$ ) participating in a 12-week, open-label trial of the SRI venlafaxine for major depression, serum markers of bone formation (P1NP) and resorption (beta-CTX) were assayed before and after treatment. Participants were genotyped for putative high- versus low-expressing polymorphisms in the serotonin transporter (5HTTLPR) and 1B receptor (HTR1B) genes. Results. Bone formation was significantly reduced with administration of venlafaxine in participants with the high-expressing 5HTTLPR genotype and those with the low-expressing HTR1B genotype. This primarily occurred in individuals with the combination of the high-expressing 5HTTLPR genotype and the low-expressing HTR1B genotype. Conclusions. These preliminary findings indicate that genetic variation in the serotonin receptors predicts changes in bone metabolism during SRI use. If these results are replicated and clinically confirmed, we will have identified a genetic subgroup at high risk for deleterious bone outcomes with the use of SRIs.

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[939]

**TÍTULO / TITLE:** - Digitoflavone Inhibits I $\kappa$ B Kinase and Enhances Apoptosis Induced by TNF $\alpha$  through Downregulation of Expression of Nuclear Factor  $\kappa$ B-Regulated Gene Products in Human Pancreatic Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 11;8(10):e77126. doi: 10.1371/journal.pone.0077126.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0077126](#)

**AUTORES / AUTHORS:** - Cai X; Lu W; Yang Y; Yang J; Ye J; Gu Z; Hu C; Wang X; Cao P

**INSTITUCIÓN / INSTITUTION:** - Jiangsu Branch of China Academy of Chinese Medical Sciences, Nanjing, China ; Laboratory of Cellular and Molecular Biology, Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, China.

**RESUMEN / SUMMARY:** - Tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) activates both cell death and cell survival pathways. The activation of survival pathway renders most cancer cells resistant to TNF-induced cytotoxicity. We found that pretreatment with digitoflavone, a plant flavonoid, greatly sensitized TNF $\alpha$ -induced apoptotic cell death in several human pancreatic cancer cells. In search of the molecular basis of the sensitization effect of digitoflavone, digitoflavone was found to inhibit TNF $\alpha$ -induced activation of nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B) which is the main survival factor in TNF $\alpha$  signaling. NF- $\kappa$ B suppression occurred through inhibition of I $\kappa$ B kinase activation, I $\kappa$ B phosphorylation, I $\kappa$ B degradation, and NF- $\kappa$ B nuclear translocation. This inhibition correlated with suppression of NF- $\kappa$ B-dependent genes involved in antiapoptosis (mcl-1, bcl-2, bcl-xl, c-iap1, c-iap2, flip, and survivin), proliferation (c-myc, cyclin d1), and angiogenesis (vegf, cox-2, and mmp-9). In addition, digitoflavone can activate JNK through inhibition of NF- $\kappa$ B signaling, provide a continuous blockade of the feedback inhibitory mechanism by JNK-induced NF- $\kappa$ B activation. This study found a novel function of digitoflavone and enhanced the value of digitoflavone as an anticancer agent.

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[940]

**TÍTULO / TITLE:** - Prolonged response of relapsed high grade serous ovarian carcinoma to the oral angiokinase inhibitor nintedanib in a patient with a germline mutation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Gynecol Oncol Case Rep. 2013 Jan 1;3. pii: [1016/j.gynor.2012.10.003](#).

**AUTORES / AUTHORS:** - Wong HH; Parkinson C; Ledermann JA; Brenton JD; Merger M; Shaw A; Patterson A; Shafi M; Earl HM

**INSTITUCIÓN / INSTITUTION:** - Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK.

[941]

**TÍTULO / TITLE:** - Inhibition of mTORC1 by SU6656, the selective Src kinase inhibitor, is not accompanied by activation of Akt/PKB signalling in melanoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Folia Biol (Praha). 2013;59(4):162-7.

**AUTORES / AUTHORS:** - Ondrusova L; Reda J; Zakova P; Tuhackova Z

**INSTITUCIÓN / INSTITUTION:** - Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic.

**RESUMEN / SUMMARY:** - The mammalian target of rapamycin (mTOR) is a Ser/Thr protein kinase conserved in all eukaryotes that plays a key role in cell growth and is a central effector of several pathways regulating essential cell functions. Hyperactivation of the mTORdependent signalling pathway occurs in many human diseases and may be a selective target for their therapy. However, the dual nature of mTOR, existing in two multiprotein complexes mTORC1 and mTORC2 driven by different feedback loops, decreases the therapeutic effects of rapamycin, the specific mTOR inhibitor. In the present study we demonstrate that the mTORC1 signalling pathway is highly activated in human melanoma cells and that up-regulation of this pathway along with the growth and malignancy of these cells could be suppressed by disruption of the Src activity. SU6656, the selective inhibitor of the Src kinase activity, decreased up-regulation of the mTORC1 signalling and moreover, unlike rapamycin, it did not induce the activation of Akt/PKB and its downstream targets in HBL melanoma cells. The Src protein was found to be associated with raptor in the mTORC1 complex immunoprecipitated from these cells, suggesting that the Src activity might be a new attractive target for monotherapeutic inhibition of the up-regulated mTORC1 signalling pathway.

[942]

**TÍTULO / TITLE:** - Hispolon from *Phellinus linteus* Induces G0/G1 Cell Cycle Arrest and Apoptosis in NB4 Human Leukaemia Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Chin Med. 2013;41(6):1439-57. doi: [10.1142/S0192415X13500961](#).

●● [Enlace al texto completo \(gratis o de pago\) 1142/S0192415X13500961](#)

**AUTORES / AUTHORS:** - Chen YC; Chang HY; Deng JS; Chen JJ; Huang SS; Lin IH; Kuo WL; Chao W; Huang GJ

**INSTITUCIÓN / INSTITUTION:** - School of Post-Baccalaureate Chinese Medicine, Tzu Chi University, Hualien 970, Taiwan.

**RESUMEN / SUMMARY:** - Hispolon (a phenolic compound isolated from *Phellinus linteus*) has been shown to possess strong antioxidant, anti-inflammatory, anticancer, and antidiabetic properties. In this study, we investigated the antiproliferative effect of hispolon on human hepatocellular carcinoma NB4 cells using the MTT assay, DNA fragmentation, DAPI (4, 6-diamidino-2-phenylindole dihydrochloride) staining, and flow cytometric analysis. Hispolon inhibited the cellular growth of NB4 cells in a dose-dependent manner through the induction of cell cycle arrest at G0/G1 phase measured using flow cytometric analysis and apoptotic cell death, as demonstrated by DNA laddering. Exposure of NB4 cells to hispolon-induced apoptosis-related protein expressions, such as the cleavage form of caspase 3, caspase 8, caspase 9, poly (ADP ribose) polymerase, and the proapoptotic Bax protein. Western blot analysis showed that the protein levels of extrinsic apoptotic proteins (Fas and FasL), intrinsic related proteins (cytochrome c), and the ratio of Bax/Bcl-2 were increased in NB4 cells after hispolon treatment. Hispolon-induced G0/G1-phase arrest was associated with a marked decrease in the protein expression of p53, cyclins D1, and cyclins E, and cyclin-dependent kinases (CDKs) 2, and 4, with concomitant induction of p21waf1/Cip1 and p27Kip1. We conclude that hispolon induces both of extrinsic and intrinsic apoptotic pathways in NB4 human leukemia cells in vitro.

[943]

**TÍTULO / TITLE:** - Cytotoxic effect and induction of apoptosis in human cervical cancer cells by *Antrodia camphorata*.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Am J Chin Med. 2013;41(5):1169-80. doi: 10.1142/S0192415X13500791.

●● [Enlace al texto completo \(gratis o de pago\) 1142/S0192415X13500791](#)

**AUTORES / AUTHORS:** - Yang PY; Hu DN; Liu FS

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Research, Show Chwan Memorial Hospital, Changhua, Taiwan, ROC.

**RESUMEN / SUMMARY:** - *Antrodia camphorata* is a Chinese herb indigenous to Taiwan. Previous reports demonstrated that it could induce apoptosis in some cancer cells. The purpose of this study was to investigate the apoptotic effect of the crude extract of *A. camphorata* in cervical cancer cells. Two human cervical cancer cell lines, HeLa and C-33A, were treated with extract of *A. camphorata* (10-1000 µg/mL). We found that *A. camphorata* extract was cytotoxic to both cervical cancer cells in a dose- and time-dependent manner as examined by MTT assay. Treatment with *A. camphorata* extract at 400 µg/mL induced a 2.3- and 4.4-fold increase in oligonucleosome formation from the cleaved chromosomal DNA in HeLa and C-33A cells, respectively. *A. camphorata* extract also activated caspase-3, -8, and -9 activities and increased the cytosolic level of cytochrome c in both cell lines as the dosage increased. Furthermore, *A. camphorata* extract increased expressions of Bak, Bad and Bim, while decreasing expressions of Bcl-2 and Bcl-xL of the Bcl-2 family proteins in HeLa and C-33A cells. The expression of IAP proteins, XIAP and survivin, was also decreased in both cervical cancer cells after treatment with *A. camphorata*. Our in vitro study suggests that *A. camphorata* is cytotoxic to cervical cancer cells through both

extrinsic and intrinsic apoptotic mechanisms. It could be used as a novel phytotherapeutic agent or auxiliary therapy in the treatment of cervical cancer.

[944]

**TÍTULO / TITLE:** - Prognostic value of isocitrate dehydrogenase 1, O6-methylguanine-DNA methyltransferase promoter methylation, and 1p19q co-deletion in Japanese malignant glioma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - World J Surg Oncol. 2013 Oct 25;11(1):284.

●● Enlace al texto completo (gratis o de pago) [1186/1477-7819-11-284](#)

**AUTORES / AUTHORS:** - Takahashi Y; Nakamura H; Makino K; Hide T; Muta D; Kamada H; Kuratsu JI

**RESUMEN / SUMMARY:** - BACKGROUND: To determine the prognostic value of isocitrate dehydrogenase 1 (IDH1) mutation, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and 1p/19q co-deletion in Japanese patients with malignant gliomas. METHODS: We studied 267 malignant gliomas, which included 171 glioblastomas (GBMs), 40 anaplastic astrocytomas (AAs), 30 anaplastic oligodendrogliomas (AOs), and 26 anaplastic oligoastrocytomas (AOAs). These malignant gliomas were divided into 2 groups (Group 1: GBM + AA, Group 2: AO + AOA) according to the presence of the oligodendroglioma component. We examined IDH1 mutation and MGMT promoter methylation in each group by direct sequencing and methylation-specific PCR, respectively. We further examined 1p/19q co-deletion in Group 2 by fluorescence in situ hybridization. Survival between groups was compared by Kaplan—Meier analysis. RESULTS: In Group 1, patients with IDH1 mutations exhibited a significantly longer survival time than patients with wild-type IDH1. However, no significant difference was observed in Group 2, although patients with IDH mutations tended to show prolonged survival. For both Group 1 and Group 2, patients with MGMT methylation survived longer than those without this methylation. Further, patients with 1p/19q co-deletion showed significantly better outcome in Group 2. CONCLUSIONS: Our study confirms the utility of IDH1 mutations and MGMT methylation in predicting the prognosis of Group 1 patients (GBM + AA) and demonstrated that IDH1 mutations may serve as a more reliable prognostic factor for such patients. We also showed that MGMT methylation and 1p/19q co-deletion rather than IDH1 mutations were prognostic factors for Group 2 patients (AOA + AO). Our study suggests that patients survive longer if they have IDH1 mutations and undergo total resection. Further, irrespective of MGMT promoter methylation status, the prognosis of glioma patients can be improved if total resection is performed. Moreover, our study includes the largest number of Japanese patients with malignant gliomas that has been analyzed for these three markers. We believe that our findings will increase the awareness of oncologists in Japan of the value of these markers for predicting prognosis and designing appropriate therapeutic strategies for treating this highly fatal disease.

[945]

**TÍTULO / TITLE:** - New pyrazolopyrimidine inhibitors of protein kinase d as potent anticancer agents for prostate cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Sep 23;8(9):e75601. doi: 10.1371/journal.pone.0075601.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0075601](https://doi.org/10.1371/journal.pone.0075601)

**AUTORES / AUTHORS:** - Tandon M; Johnson J; Li Z; Xu S; Wipf P; Wang QJ

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America.

**RESUMEN / SUMMARY:** - The emergence of protein kinase D (PKD) as a potential therapeutic target for several diseases including cancer has triggered the search for potent, selective, and cell-permeable small molecule inhibitors. In this study, we describe the identification, in vitro characterization, structure-activity analysis, and biological evaluation of a novel PKD inhibitory scaffold exemplified by 1-naphthyl PP1 (1-NA-PP1). 1-NA-PP1 and IKK-16 were identified as pan-PKD inhibitors in a small-scale targeted kinase inhibitor library assay. Both screening hits inhibited PKD isoforms at about 100 nM and were ATP-competitive inhibitors. Analysis of several related kinases indicated that 1-NA-PP1 was highly selective for PKD as compared to IKK-16. SAR analysis showed that 1-NA-PP1 was considerably more potent and showed distinct substituent effects at the pyrazolopyrimidine core. 1-NA-PP1 was cell-active, and potently blocked prostate cancer cell proliferation by inducing G2/M arrest. It also potently blocked the migration and invasion of prostate cancer cells, demonstrating promising anticancer activities on multiple fronts. Overexpression of PKD1 or PKD3 almost completely reversed the growth arrest and the inhibition of tumor cell invasion caused by 1-NA-PP1, indicating that its anti-proliferative and anti-invasive activities were mediated through the inhibition of PKD. Interestingly, a 12-fold increase in sensitivity to 1-NA-PP1 could be achieved by engineering a gatekeeper mutation in the active site of PKD1, suggesting that 1-NA-PP1 could be paired with the analog-sensitive PKD1(M659G) for dissecting PKD-specific functions and signaling pathways in various biological systems.

[946]

**TÍTULO / TITLE:** - Decreased levels of serum cytokeratin 19 fragment CYFRA 21-1 predict objective response to chemotherapy in patients with non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Ther Med. 2013 Aug;6(2):355-360. Epub 2013 Jun 20.

●● Enlace al texto completo (gratis o de pago) [3892/etm.2013.1171](https://doi.org/10.1371/journal.pone.0075601)

**AUTORES / AUTHORS:** - Pang L; Wang J; Jiang Y; Chen L

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Chinese PLA General Hospital, Beijing 100853;

**RESUMEN / SUMMARY:** - Diagnostic tools capable of predicting early responses to chemotherapy are required to improve the individual management of cancer patients. The present study aimed to evaluate the prognostic significance of the serum tumor markers CYFRA 21-1, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), carbohydrate antigen (CA) 125, and CA 19-9 for predicting responses to different chemotherapy regimens in patients with non-small cell lung cancer (NSCLC). A total of 276 patients with postoperative stage I-IV NSCLC were retrospectively reviewed. The five tumor markers were measured before and after at least two cycles of chemotherapy using an electrochemiluminescent assay. Multivariate analysis revealed that performance status, age, postoperative stage and surgery were significantly associated with the response to chemotherapy. High baseline CYFRA 21-1

and CA 19-9 levels were associated with poor effectiveness of chemotherapy. Significant reductions in CYFRA 21-1 levels were associated with a positive response to various chemotherapy regimens. CEA, CA 125 and CA 19-9 expression was only associated with a positive response in patients receiving paclitaxel, docetaxel, pemetrexed and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). NSE expression was only associated with a positive response to gemcitabine. Receiver operating characteristic (ROC) curve analysis indicated that CYFRA 21-1 is the most sensitive of the tumor markers in predicting the response to chemotherapy. Serum CYFRA 21-1 is a useful surrogate marker for predicting the response to different chemotherapy regimens used to treat NSCLC and is a more sensitive marker than CEA, CA125, CA19-9 and NSE.

[947]

**TÍTULO / TITLE:** - High Coexpression of Both EGFR and IGF1R Correlates With Poor Patient Prognosis in Resected Non-Small-Cell Lung Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Lung Cancer. 2013 Nov 7. pii: S1525-7304(13)00182-4. doi: 10.1016/j.clcc.2013.08.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.clcc.2013.08.005](#)

**AUTORES / AUTHORS:** - Gately K; Forde L; Cuffe S; Cummins R; Kay EW; Feuerhake F; O'Byrne KJ

**INSTITUCIÓN / INSTITUTION:** - Thoracic Oncology Research Group, Institute of Molecular Medicine, Trinity College Dublin, St. James's Hospital, Dublin, Ireland. Electronic address: [kgately@stjames.ie](mailto:kgately@stjames.ie).

**RESUMEN / SUMMARY:** - BACKGROUND: Recent experimental and biomarker evidence indicates that the epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor 1 (IGF1R) interact in the pathogenesis of malignant epithelial tumors, including lung cancer. This study examines the expression of both receptors and their prognostic significance in surgically resected non-small-cell lung cancer (NSCLC). METHODS: EGFR and IGF1R expression were evaluated in 184 patients with NSCLC (83 squamous cell carcinomas [SCCs], 83 adenocarcinomas [ADCs], and 18 other types) using immunohistochemical (IHC) analysis. Expression of both receptors was examined in matched fresh frozen normal and tumor tissues from 40 patients with NSCLC (20 SCCs and 20 ADCs) by Western blot analysis. RESULTS: High EGFR expression was detected in 51% of patients, and SCCs had higher EGFR expression than did non-SCCs (57.4% vs. 42.5%;  $P = .028$ ). High IGF1R expression was observed in 53.8% of patients, with SCC having higher expression than non-SCC (62.6% vs. 37.3%;  $P = .0004$ ). A significant association was shown between EGFR and IGF1R protein overexpression ( $P < .005$ ). Patients with high expression of both receptors had a poorer overall survival (OS) ( $P = .04$ ). Higher EGFR and IGF1R expression was detected in resected tumors relative to matched normal tissues ( $P = .0004$  and  $P = .0009$ ), with SCC having higher expression levels than ADC. CONCLUSION: Our findings indicate a close interrelationship between EGFR and IGF1R. Coexpression of both receptors correlates with poor survival. This subset of patients may benefit from treatments cotargeting EGFR and IGF1R.

[948]

**TÍTULO / TITLE:** - Curcumin Suppresses Malignant Glioma Cells Growth and Induces Apoptosis by Inhibition of SHH/GLI1 Signaling Pathway in Vitro and Vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - CNS Neurosci Ther. 2013 Dec;19(12):926-36. doi: 10.1111/cns.12163. Epub 2013 Oct 25.

●● Enlace al texto completo (gratis o de pago) [1111/cns.12163](#)

**AUTORES / AUTHORS:** - Du WZ; Feng Y; Wang XF; Piao XY; Cui YQ; Chen LC; Lei XH; Sun X; Liu X; Wang HB; Li XF; Yang DB; Sun Y; Zhao ZF; Jiang T; Li YL; Jiang CL

**INSTITUCIÓN / INSTITUTION:** - Department of Neurosurgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, China.

**RESUMEN / SUMMARY:** - AIMS: To study the role of curcumin on glioma cells via the SHH/GLI1 pathway in vitro and vivo. METHODS: The effects of curcumin on proliferation, migration, apoptosis, SHH/GLI1 signaling, and GLI1 target genes expression were evaluated in multiple glioma cell lines in vitro. A U87-implanted nude mice model was used to study the role of curcumin on tumor volume and the suppression efficacy of GLI1. RESULTS: Curcumin showed cytotoxic effects on glioma cell lines in vitro. Both mRNA and protein levels of SHH/GLI1 signaling (Shh, Smo, GLI1) were downregulated in a dose- and time-dependent manner. Several GLI1-dependent target genes (CyclinD1, Bcl-2, Foxm1) were also downregulated. Curcumin treatment prevented GLI1 translocating into the cell nucleus and reduced the concentration of its reporter. Curcumin suppressed cell proliferation, colony formation, migration, and induced apoptosis which was mediated partly through the mitochondrial pathway after an increase in the ratio of Bax to Bcl2. Intraperitoneal injection of curcumin in vivo reduced tumor volume, GLI1 expression, the number of positively stained cells, and prolonged the survival period compared with the control group. CONCLUSION: This study shows that curcumin holds a great promise for SHH/GLI1 targeted therapy against gliomas.

[949]

**TÍTULO / TITLE:** - Two-Week Combination Chemotherapy with Gemcitabine, High-Dose Folinic Acid and 5 Fluorouracil (GEMFUFOL) as First-Line Treatment of Metastatic Biliary Tract Cancers.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):5263-7.

**AUTORES / AUTHORS:** - Unal OU; Oztop I; Unek IT; Yilmaz AU

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Medical Faculty, Ataturk University, Erzurum, Turkey E-mail : [drolcun@hotmail.com](mailto:drolcun@hotmail.com).

**RESUMEN / SUMMARY:** - Background: The aim of this study was to evaluate the efficacy and tolerability of a gemcitabine, 5-fluorouracil and leucovorin (GEMFUFOL) chemotherapy regimen as first line treatment of metastatic biliary tract cancer. Materials and Methods: All patients received folinic acid 400 mg/m<sup>2</sup> on day 1, 5-fluorouracil bolus 400 mg/ m<sup>2</sup> on day 1, IV infusion of 5-fluorouracil 2400 mg/m<sup>2</sup> over 46 hours, and gemcitabine 1250 mg/m<sup>2</sup> on day 1. Results: A total of 29 patients with metastatic biliary tract cancer received GEMFUFOL regimen as the first- line treatment. The mean follow-up was 22.1 months (95%CI, 12.5-31.8). One patient (3.4%) achieved complete response, 5 (17.2%) had partial response, and 4 (13.8%) had stable disease. The median progression-free survival was 3.3 months (95%CI, 2.9-3.7), and the median overall survival was 8.8 months (95%CI, 3.5-14). The 1-year and 2-year

survival rates were 58.6% and 30%, respectively. Grade 3 and 4 toxicity included neutropenia in 4 patients (13.7%), thrombocytopenia in 2 (6.8%), anemia in 2 (6.8%), and alopecia in 1 (3.4%). Two patients (6.8%) developed febrile neutropenia. A dose reduction was achieved in 8 patients (27.6%) while 5 patients had extended-interval dosage (17.2%) for toxicity. Conclusions: The GEMFUFOL chemotherapy regimen was generally efficacious and tolerable as a first-line treatment of metastatic biliary tract cancer.

[950]

**TÍTULO / TITLE:** - EBUS-TBNA Provides Highest RNA Yield for Multiple Biomarker Testing from Routinely Obtained Small Biopsies in Non-Small Cell Lung Cancer Patients - A Comparative Study of Three Different Minimal Invasive Sampling Methods.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 29;8(10):e77948. doi: 10.1371/journal.pone.0077948.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0077948](#)

**AUTORES / AUTHORS:** - Schmid-Bindert G; Wang Y; Jiang H; Sun H; Henzler T; Wang H; Pilz LR; Ren S; Zhou C

**INSTITUCIÓN / INSTITUTION:** - Department of Surgery, University Medical Center Mannheim, Medical Faculty Mannheim of Heidelberg University, Mannheim, Germany.

**RESUMEN / SUMMARY:** - BACKGROUND: Multiple biomarker testing is necessary to facilitate individualized treatment of lung cancer patients. More than 80% of lung cancers are diagnosed based on very small tumor samples. Often there is not enough tissue for molecular analysis. We compared three minimal invasive sampling methods with respect to RNA quantity for molecular testing. METHODS: 106 small biopsies were prospectively collected by three different methods forceps biopsy, endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA), and CT-guided core biopsy. Samples were split into two halves. One part was formalin fixed and paraffin embedded for standard pathological evaluation. The other part was put in RNAlater for immediate RNA/DNA extraction. If the pathologist confirmed the diagnosis of non-small cell lung cancer(NSCLC), the following molecular markers were tested: EGFR mutation, ERCC1, RRM1 and BRCA1. RESULTS: Overall, RNA-extraction was possible in 101 out of 106 patients (95.3%). We found 49% adenocarcinomas, 38% squamouscarcinomas, and 14% non-otherwise-specified(NOS). The highest RNA yield came from endobronchial ultrasound guided needle aspiration, which was significantly higher than bronchoscopy (37.74+/-41.09 vs. 13.74+/-15.53 ng respectively, P = 0.005) and numerically higher than CT-core biopsy (37.74+/-41.09 vs. 28.72+/-44.27 ng respectively, P = 0.244). EGFR mutation testing was feasible in 100% of evaluable patients and its incidence was 40.8%, 7.9% and 14.3% in adenocarcinomas, squamouscarcinomas and NSCLC NOS subgroup respectively. There was no difference in the feasibility of molecular testing between the three sampling methods with feasibility rates for ERCC1, RRM1 and BRCA1 of 91%, 87% and 81% respectively. CONCLUSION: All three methods can provide sufficient tumor material for multiple biomarkers testing from routinely obtained small biopsies in lung cancer patients. In our study EBUS guided needle aspiration provided the highest amount of tumor RNA compared to bronchoscopy or CT guided core biopsy. Thus EBUS should be considered as an acceptable option for tissue acquisition for molecular testing.

[951]

**TÍTULO / TITLE:** - MicroRNA-Gene Association As a Prognostic Biomarker in Cancer Exposes Disease Mechanisms.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS Comput Biol. 2013 Nov;9(11):e1003351. doi: 10.1371/journal.pcbi.1003351. Epub 2013 Nov 21.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pcbi.1003351](#)

**AUTORES / AUTHORS:** - Ben-Hamo R; Efroni S

**INSTITUCIÓN / INSTITUTION:** - The Mina and Everard Goodman Faculty of Life Science, Bar Ilan University, Ramat-Gan, Israel.

**RESUMEN / SUMMARY:** - The transcriptional networks that regulate gene expression and modifications to this network are at the core of the cancer phenotype. MicroRNAs, a well-studied species of small non-coding RNA molecules, have been shown to have a central role in regulating gene expression as part of this transcriptional network. Further, microRNA deregulation is associated with cancer development and with tumor progression. Glioblastoma Multiform (GBM) is the most common, aggressive and malignant primary tumor of the brain and is associated with one of the worst 5-year survival rates among all human cancers. To study the transcriptional network and its modifications in GBM, we utilized gene expression, microRNA sequencing, whole genome sequencing and clinical data from hundreds of patients from different datasets. Using these data and a novel microRNA-gene association approach we introduce, we have identified unique microRNAs and their associated genes. This unique behavior is composed of the ability of the quantifiable association of the microRNA and the gene expression levels, which we show stratify patients into clinical subgroups of high statistical significance. Importantly, this stratification goes unobserved by other methods and is not affiliated by other subsets or phenotypes within the data. To investigate the robustness of the introduced approach, we demonstrate, in unrelated datasets, robustness of findings. Among the set of identified microRNA-gene associations, we closely study the example of MAF and hsa-miR-330-3p, and show how their co-behavior stratifies patients into prognosis clinical groups and how whole genome sequences tells us more about a specific genomic variation as a possible basis for patient variances. We argue that these identified associations may indicate previously unexplored specific disease control mechanisms and may be used as basis for further study and for possible therapeutic intervention.

[952]

**TÍTULO / TITLE:** - Effect of variation of ABCB1 and ABCC3 genotypes on the survival of bone tumor cases after chemotherapy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(8):4595-8.

**AUTORES / AUTHORS:** - Yang J; Wang ZG; Cai HQ; Li YC; Xu YL

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Orthopedics, Shanghai Children's Medical Center, Shanghai Jiaotong University, Shanghai, China E-mail : [xuyuanlan699@126.com](mailto:xuyuanlan699@126.com).

**RESUMEN / SUMMARY:** - We conducted a comprehensive study to investigate the role of genes involved in transport pathways in response to chemotherapy and clinical outcome of osteosarcoma cases. Genotyping of six SNPs was performed in a 384-well

plate format on the Sequenom MassARRAY platform for 208 osteosarcoma patients to reveal any correlations of the six SNPs with response to chemotherapy and clinical outcome. Individuals with the ABCB1 rs1128503 TT and ABCC3 rs4148416 TT genotypes had a higher probability of responding poorly to chemotherapy, indicated by odds ratios (ORs) of 2.46 (95%CI, 1.21-5.74) and 3.78 (95% CI, 1.20-13.85), respectively. Moreover, the ABCB1 rs1128503 TT and ABCC3 rs4148416 TT genotypes were significantly associated with shorter disease-free survival (DFS) and overall survival (OS). Our study found the two SNPs in two transporter genes and one phase II metabolism enzyme to be associated with response to chemotherapy and overall survival in osteosarcoma patients, suggesting potential prognostic biomarker applications of the two SNPs.

[953]

**TÍTULO / TITLE:** - Antioxidants may protect cancer cells from apoptosis signals and enhance cell viability.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(8):4611-4.

**AUTORES / AUTHORS:** - Akan Z; Garip AI

**INSTITUCIÓN / INSTITUTION:** - Department of Biophysics, School of Medicine, Yuzuncu Yil University, Van, Turkey E-mail : [zafer\\_akan@hotmail.com](mailto:zafer_akan@hotmail.com).

**RESUMEN / SUMMARY:** - Quercetin is one of the most abundant dietary flavonoids widely present in many fruits and vegetables. Previous in vitro studies has shown that quercetin acts as an antioxidant and anti-inflammatory agent and it has potent anticarcinogenic properties as an apoptosis inducer. In this study we examined apoptotic effects of quercetin on the K562 erythroleukemia cell line. K562 cells were induced to undergo apoptosis by hydrogen peroxide. Cell viability and apoptosis level were assessed by annexin V and PI staining methods using flow cytometry. Viability of K562 cells was increased by low dose of quercetin (5-100 µM) for 3 hours. High doses of quercetin proved toxic (100-500 µM, 24 hours) and resulted in decrease of K562 cell viability as expected (P<0.01). As to results, 100 µM quercetin was defined as a protective dose. Also, K562 cell apoptosis due to hydrogen peroxide was decreased in a dose dependent manner. As indicated in previous studies, reduction of superoxides by free radical scavengers like quercetin could be beneficial for prevention of cancer but consumption of such flavonoids during cancer treatment may weaken effects of chemotherapeutics and radiotherapy. Especially cancer patients should be carefully considered for traditional phytotherapy during cancer treatment, which can lead to controversial results.

[954]

**TÍTULO / TITLE:** - Endogenous cystathionine-gamma-lyase/hydrogen sulfide pathway regulates apoptosis of HepG2 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Yao Xue Xue Bao. 2013 Aug;48(8):1233-40.

**AUTORES / AUTHORS:** - Wang TX; Shi XY; Liu YH

**INSTITUCIÓN / INSTITUTION:** - Institute of Chinese Materia Medica, College of Pharmacy, Henan University, Kaifeng 475004, China. [wtx1975@126.com](mailto:wtx1975@126.com)

**RESUMEN / SUMMARY:** - This study is to investigate the role of endogenous CSE/H<sub>2</sub>S in regulating apoptosis of HepG2 cells. MTT and Trypan blue assay were performed to determine the effect of CSE inhibitor PAG and CSE siRNA on proliferation of HepG2. Production of H<sub>2</sub>S from HepG2 cells was assessed spectrophotometrically using N, N-dimethyl-p-phenylenediamine-dihydrochloride. Cells apoptosis was detected by means of double staining of Hoechst 33342 and PI with Array Scan V(TI)HCS600 High-Contents. Dihydroethidine (DHE) and 2', 7'-dichlorodihydrofluorescein diacetate (DCFH-DA) assay was used to determine intracellular superoxide anion and ROS level. Reduced glutathione (GSH) was determined by OxiSelect Total Glutathione Assay Kit. Recombinant plasmid pcDNA 3.1/myc-His(-)-CSE was constructed and transfected into 293T cells to rescue the ROS and GSH level to further investigate the effect of CSE/H<sub>2</sub>S on ROS and GSH. Western blotting was performed to test the effect of CSE siRNA on expression of activated caspase 3 and p-AKT and Nrf2 protein. The results showed that PAG and CSE siRNA could significantly decrease the production of H<sub>2</sub>S in HepG2 cells and inhibit the proliferation of HepG2 cells at a dose-dependent and time-dependent manner, respectively. PAG and CSE siRNA could promote the cell apoptosis of HepG2 cells. Moreover, PAG and CSE siRNA induced increased ROS generation and depletion of the critical antioxidant GSH and recombinant plasmid pcDNA 3.1/myc-His(-)-CSE rescued the level of ROS and GSH. Meanwhile, CSE siRNA increased the expression of activated caspase 3, but CSE siRNA did not affect the expression of p-AKT and Nrf2. These results suggested that the CSE/H<sub>2</sub>S pathway was involved in suppression of HepG2 cell growth and promoted apoptosis of HepG2 cells in an oxidative stress-dependent manner.

[955]

**TÍTULO / TITLE:** - Rapid reuptake of granzyme B leads to emperitosis: an apoptotic cell-in-cell death of immune killer cells inside tumor cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Oct 10;4:e856. doi: 10.1038/cddis.2013.352.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.352](#)

**AUTORES / AUTHORS:** - Wang S; He MF; Chen YH; Wang MY; Yu XM; Bai J; Zhu HY; Wang YY; Zhao H; Mei Q; Nie J; Ma J; Wang JF; Wen Q; Ma L; Wang Y; Wang XN

**INSTITUCIÓN / INSTITUTION:** - 1] The Institute of Life Sciences, Chinese PLA General Hospital and South China University of Technology, The State Key Laboratory of Kidney Disease, Beijing 100853, China, The Provincial Key Laboratory of Biotechnology, Guangzhou 510006, China [2] The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510260, China.

**RESUMEN / SUMMARY:** - A cell-in-cell process refers to the invasion of one living cell into another homotypic or heterotypic cell. Different from non-apoptotic death processes of internalized cells termed entosis or cannibalism, we previously reported an apoptotic cell-in-cell death occurring during heterotypic cell-in-cell formation. In this study, we further demonstrated that the apoptotic cell-in-cell death occurred only in internalized immune killer cells expressing granzyme B (GzmB). Vacuole wrapping around the internalized cells inside the target cells was the common hallmark during the early stage of all cell-in-cell processes, which resulted in the accumulation of reactive oxygen species and subsequent mitochondrial injury of encapsulated killer or

non-cytotoxic immune cells. However, internalized killer cells mediated rapid bubbling of the vacuoles with the subsequent degranulation of GzmB inside the vacuole of the target cells and underwent the reuptake of GzmB by killer cells themselves. The confinement of GzmB inside the vacuole surpassed the lysosome-mediated cell death occurring in heterotypic or homotypic entosis processes, resulting in a GzmB-triggered caspase-dependent apoptotic cell-in-cell death of internalized killer cells. On the contrary, internalized killer cells from GzmB-deficient mice underwent a typical non-apoptotic entotic cell-in-cell death similar to that of non-cytotoxic immune cells or tumor cells. Our results thus demonstrated the critical involvement of immune cells with cytotoxic property in apoptotic cell-in-cell death, which we termed as emperitosis taken from emperipolosis and apoptosis. Whereas entosis or cannibalism may serve as a feed-on mechanism to exacerbate and nourish tumor cells, emperitosis of immune killer cells inside tumor cells may serve as an in-cell danger sensation model to prevent the killing of target cells from inside, implying a unique mechanism for tumor cells to escape from immune surveillance.

[956]

**TÍTULO / TITLE:** - Correlation between ER, PR, HER-2, Bcl-2, p53, proliferative and apoptotic indexes with HER-2 gene amplification and TOP2A gene amplification and deletion in four molecular subtypes of breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Target Oncol. 2013 Nov 24.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11523-013-0297-2](#)

**AUTORES / AUTHORS:** - Mitrovic O; Cokic V; Dikic D; Budec M; Vignjevic S; Suboticki T; Gulan M; Radovic S; Furtula S

**INSTITUCIÓN / INSTITUTION:** - Institute for Medical Research, University of Belgrade, Dr Subotica 4, PO Box 39, 11129, Belgrade 102, Serbia, [oliveram@imi.bg.ac.rs](mailto:oliveram@imi.bg.ac.rs).

**RESUMEN / SUMMARY:** - The aim of our study was to investigate HER-2 and TOP2A gene status and their correlation with Bcl-2, p53, Ki67, ssDNA, and clinicopathological parameters in four molecular subtypes of breast cancer. Seventy-four paraffin-embedded samples are immunohistochemically studied for the expression of estrogen receptor (ER), progesterone receptor (PR), HER-2, p53, Bcl-2, ssDNA, and Ki67, while HER-2 and TOP2A gene status by fluorescence in situ hybridization was investigated in 60 samples. Luminal A and B subtypes were characterized with small tumor size, intermediate histological grade, negative lymph node, and metastatic status, while triple negative and HER-2 positive subtypes were associated with larger tumor size, poorly differentiated tumors, and positive lymph node status. p53, Ki67, and ssDNA expression was higher in triple negative and HER-2 positive than in luminal subtypes, while ER, PR, and Bcl-2 dominated in luminal subtypes. HER-2 gene status was higher in luminal B and HER-2 positive than in luminal A and triple negative subtypes, while TOP2A gene status was similar. HER-2 gene status positively correlated with TOP2A gene status, HER-2 receptor, and histological grade, while negative correlation characterized relationship between HER-2 gene status and ER, PR, and Bcl-2. The shortened overall survival period characterized patients from triple negative breast cancer subtype (18.7 months). HER-2 and TOP2A gene amplification showed a tendency to be associated with larger tumor size, positive lymph node status, high level of apoptotic and proliferative indexes, and low level of p53 and Bcl-2 expression, which

all together indicate group of patients with similar outcome during the progression of the disease.

[957]

**TÍTULO / TITLE:** - Concomitant EGFR inhibitors combined with radiation for treatment of non-small cell lung carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(8):4485-94.

**AUTORES / AUTHORS:** - Zheng DJ; Yu GH; Gao JF; Gu JD

**INSTITUCIÓN / INSTITUTION:** - Department of Clinical Oncology, Weifang People's Hospital, Weifang, China E-mail : [jundonggu@aliyun.com](mailto:jundonggu@aliyun.com).

**RESUMEN / SUMMARY:** - Epidermal growth factor receptor (EGFR) is considered to be one of the key driver genes in non-small cell lung cancer (NSCLC). Several clinical trials have shown great promise of EGFR tyrosine kinase inhibitors (TKIs) in the first-line treatment of NSCLC. Many advances have been made in the understanding of EGFR signal transduction network and the interaction between EGFR and tumor microenvironment in mediating cancer survival and development. The concomitant targeted therapy and radiation is a new strategy in the treatment of NSCLC. A number of preclinical studies have demonstrated synergistic anti-tumor activity in the combination of EGFR inhibitors and radiotherapy in vitro and in vivo. In the present review, we discuss the rationale of the combination of EGFR inhibitors and radiotherapy in the treatment of NSCLC.

[958]

**TÍTULO / TITLE:** - A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Prostate Cancer Prostatic Dis. 2013 Oct 22. doi: 10.1038/pcan.2013.49.

●● [Enlace al texto completo \(gratis o de pago\) 1038/pcan.2013.49](#)

**AUTORES / AUTHORS:** - Ross AE; Feng FY; Ghadessi M; Erho N; Crisan A; Buerki C; Sundi D; Mitra AP; Vergara IA; Thompson DJ; Triche TJ; Davicioni E; Bergstralh EJ; Jenkins RB; Karnes RJ; Schaeffer EM

**INSTITUCIÓN / INSTITUTION:** - Brady Urological Institute, John Hopkins Medical Institute, Baltimore, MD, USA.

**RESUMEN / SUMMARY:** - Background: Due to their varied outcomes, men with biochemical recurrence (BCR) following radical prostatectomy (RP) present a management dilemma. Here, we evaluate Decipher, a genomic classifier (GC), for its ability to predict metastasis following BCR. Methods: The study population included 85 clinically high-risk patients who developed BCR after RP. Time-dependent receiver operating characteristic (ROC) curves, weighted Cox proportional hazard models and decision curves were used to compare GC scores to Gleason score (GS), PSA doubling time (PSAdT), time to BCR (ttBCR), the Stephenson nomogram and CAPRA-S for predicting metastatic disease progression. All tests were two-sided with a type I error probability of 5%. Results: GC scores stratified men with BCR into those who would or would not develop metastasis (8% of patients with low versus 40% with high scores developed metastasis,  $P < 0.001$ ). The area under the curve for predicting

metastasis after BCR was 0.82 (95% CI, 0.76-0.86) for GC, compared to GS 0.64 (0.58-0.70), PSA<sub>d</sub>T 0.69 (0.61-0.77) and ttBCR 0.52 (0.46-0.59). Decision curve analysis showed that GC scores had a higher overall net benefit compared to models based solely on clinicopathologic features. In multivariable modeling with clinicopathologic variables, GC score was the only significant predictor of metastasis (P=0.003). Conclusions: When compared to clinicopathologic variables, GC better predicted metastatic progression among this cohort of men with BCR following RP. While confirmatory studies are needed, these results suggest that use of GC may allow for better selection of men requiring earlier initiation of treatment at the time of BCR. Prostate Cancer and Prostatic Disease advance online publication, 22 October 2013; doi:10.1038/pcan.2013.49.

[959]

**TÍTULO / TITLE:** - TOP2A protein by quantitative immunofluorescence as a predictor of response to epirubicin in the neoadjuvant treatment of breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 Oct;9(10):1477-87. doi: 10.2217/fon.13.103.

●● Enlace al texto completo (gratis o de pago) [2217/fon.13.103](#)

**AUTORES / AUTHORS:** - Moretti E; Desmedt C; Biagioni C; Regan MM; Oakman C; Larsimont D; Galardi F; Piccart-Gebhart M; Sotiriou C; Rimm DL; Di Leo A

**INSTITUCIÓN / INSTITUTION:** - 'Sandro Pitigliani' Medical Oncology Unit, Hospital of Prato, Istituto Toscano Tumori, Piazza Ospedale 2, 59100, Prato, Italy.

**RESUMEN / SUMMARY:** - AIM: Anthracyclines are commonly used in breast cancer, although they lack validated predictive biomarkers. We explored the interaction between TOP2A protein by quantitative immunofluorescence (QIF) and anthracycline sensitivity. PATIENTS & METHODS: Patients with estrogen receptor-negative breast cancer received neoadjuvant epirubicin. Pretreatment biopsies were analyzed using AQUA®. Total, cytoplasmic (C) and nuclear (N) TOP2A protein concentrations were expressed as QIF scores and compared with pathologic complete response (pCR), TOP2A by immunohistochemistry, TOP2A mRNA, TOP2A and HER2 gene status, and Ki-67 level. RESULTS: In total, 76 cases were assessable. C, N, and total scores did not correlate with pCR, or other markers. The N:C ratio differed significantly by HER2 status. No pCRs occurred in patients in the lowest N:C quartile. CONCLUSION: Although no relevant correlation between TOP2A QIF scores and pCR was found, N:C ratio may have a negative predictive role, and may merit further exploration in a multifactorial predictive model that includes tumor and host factors.

[960]

**TÍTULO / TITLE:** - The evaluation of efficacy and safety of sunitinib on EGFR-TKI pretreated advanced Non-small cell lung cancer patients in China.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Clin Respir J. 2013 Oct 4. doi: 10.1111/crj.12059.

●● Enlace al texto completo (gratis o de pago) [1111/crj.12059](#)

**AUTORES / AUTHORS:** - Liu YR; Zhu W; Zhang JL; Huang JQ; Zhao YZ; Zhang W; Han BH; Yao YH; Jiang LY

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, 200030, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Sunitinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) exhibiting antiangiogenic and antitumor effects OBJECTIVE: To evaluate the efficacy and potential toxicity of sunitinib therapy in advanced non-small cell lung cancer NSCLC patients in china METHODS: From January 2009 to August 2011, thirty patients with stage IV NSCLC, who were pretreated with the epidermal growth factor receptor (EGFR)-TKIs and then received sunitinib, were retrospectively reviewed. Univariate and multivariate Cox proportional hazard regression analysis was performed to determine the potential prognostic risk factors influencing NSCLC survival RESULTS: The median progression-free survival (PFS) and median overall survival (OS) of all 30 treated patients was 1.25 months (95% CI: 0.90-1.9 months) and 3.40 months (95% CI: 3.00-6.80 months), respectively. Cox regression analysis suggested that Eastern Cooperative Oncology Group (ECOG) performance status (PS) is predictive of both PFS ( $p=0.001$ ) and OS ( $p<0.001$ ). Common adverse events (AEs) were reported involving hand-foot syndrome (53.3%), mucositis (40.0%), rash (36.7%) and diarrhea (33.3%). CONCLUSION: No sign of overall clinical benefits of sunitinib was detected in patients with pretreated EGFR-TKIs. Most patients suffered AEs from mild to moderate severity. ECOG PS is highly associated with PFS and OS rate. Further studies in NSCLC are required to determine whether sunitinib is beneficial nor not.

[961]

**TÍTULO / TITLE:** - RECIST 1.1 and serum thyroglobulin measurements in the evaluation of responses to sorafenib in patients with radioactive iodine-refractory differentiated thyroid carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Aug;6(2):480-486. Epub 2013 Jun 25.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ol.2013.1424](#)

**AUTORES / AUTHORS:** - Ruan M; Shen Y; Chen L; Li M

**INSTITUCIÓN / INSTITUTION:** - Department of Nuclear Medicine, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai 200233;

**RESUMEN / SUMMARY:** - The present study was designed to investigate the association between response evaluation criteria in solid tumors (RECIST) 1.1 and 1.0, and to explore the utility of thyroglobulin (Tg) measurements in assessing tumor responses to sorafenib in patients with radioactive iodine (RAI)-refractory differentiated thyroid carcinoma (DTC). In total, 23 patients with RAI-refractory DTC were enrolled. A comparison of RECIST 1.1 and 1.0 was performed in all patients with measurable disease. Following the exclusion of patients who were positive for anti-Tg antibody, the correlation between RECIST 1.1 and Tg was investigated in patients with measurable disease, and the concordance of the change in Tg between these patients and the patients with non-measurable disease only was analyzed over time. Tumor responses, assessed by RECIST 1.1 and 1.0, were concordant in 96% of the 23 records. However, the number of target lesions, according to RECIST 1.1, was significantly lower than when using RECIST 1.0. Progressive disease (PD) was identified in one of the five patients who underwent fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) scanning. A correlation between the Tg levels and the sum of the diameters of the target lesions was verified, with the percentage decrease in Tg levels significantly greater than that in the radiograph, demonstrating shrinkage. Furthermore, the percentage change in Tg levels was consistent between

the patients with measurable disease and the subjects with non-measurable disease only. In conclusion, in patients with RAI-refractory DTC, RECIST 1.1 is highly concordant with RECIST 1.0 in the assessment of responses to sorafenib treatment, with the advantage of simplified procedures and the complementary use of FDG-PET. Tg measurements, in concordance with RECIST 1.1, are valuable in the evaluation of tumor responses.

[962]

**TÍTULO / TITLE:** - Autophagy contributes to apoptosis in A20 and EL4 lymphoma cells treated with fluvastatin.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Cell Int. 2013 Nov 8;13(1):111.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-111](#)

**AUTORES / AUTHORS:** - Qi XF; Kim DH; Lee KJ; Kim CS; Song SB; Cai DQ; Kim SK

**RESUMEN / SUMMARY:** - Convincing evidence indicates that statins stimulate apoptotic cell death in several types of proliferating tumor cells in a cholesterol-lowering-independent manner. However, the relationship between apoptosis and autophagy in lymphoma cells exposed to statins remains unclear. The objective of this study was to elucidate the potential involvement of autophagy in fluvastatin-induced cell death of lymphoma cells. We found that fluvastatin treatment enhanced the activation of pro-apoptotic members such as caspase-3 and Bax, but suppressed the activation of anti-apoptotic molecule Bcl-2 in lymphoma cells including A20 and EL4 cells. The process was accompanied by increases in numbers of annexin V alone or annexin V/PI double positive cells. Furthermore, both autophagosomes and increases in levels of LC3-II were also observed in fluvastatin-treated lymphoma cells. However, apoptosis in fluvastatin-treated lymphoma cells could be blocked by the addition of 3-methyladenine (3-MA), the specific inhibitor of autophagy. Fluvastatin-induced activation of caspase-3, DNA fragmentation, and activation of LC3-II were blocked by metabolic products of the HMG-CoA reductase reaction, such as mevalonate, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These results suggest that autophagy contributes to fluvastatin-induced apoptosis in lymphoma cells, and that these regulating processes require inhibition of metabolic products of the HMG-CoA reductase reaction including mevalonate, FPP and GGPP.

[963]

**TÍTULO / TITLE:** - Phytohemagglutinin-induced IL2 mRNA in whole blood can predict bortezomib-induced peripheral neuropathy for multiple myeloma patients.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Blood Cancer J. 2013 Oct 4;3:e150. doi: 10.1038/bcj.2013.47.

●● Enlace al texto completo (gratis o de pago) [1038/bcj.2013.47](#)

**AUTORES / AUTHORS:** - Watanabe T; Mitsunashi M; Sagawa M; Ri M; Suzuki K; Abe M; Ohmachi K; Nakagawa Y; Nakamura S; Chosa M; Iida S; Kizaki M

**INSTITUCIÓN / INSTITUTION:** - Hematology Division, National Cancer Center Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** - The proteasome inhibitor bortezomib has revolutionized the treatment of multiple myeloma. However, bortezomib-induced peripheral neuropathy (BiPN) is a serious complication that compromises clinical outcome. If patients with a risk of developing BiPN could be predicted, physicians might prefer weekly, reduced-

dose, or subcutaneous approaches. To seek biomarkers for BiPN, we conducted a multicenter prospective study using a simple and unique system. Multiple myeloma patients received twice-weekly or weekly 1.3 mg/m<sup>2</sup> bortezomib intravenously, and a 2-ml sample of whole blood was obtained before treatment and 2-3 days and 1-3 weeks after the first dose. Induction of gene expression was then quantified by real-time PCR. Of a total of 64 enrolled patients, 53 patient samples qualified for mRNA analysis. The BiPN grade was associated with phytohemagglutinin-induced IL2, IFNG and TNFSF2, as well as with lipopolysaccharide-induced IL6 levels. More importantly, of the 19 patients showing a  $\geq 3$ -fold increase in phytohemagglutinin-induced IL2, 14 did not suffer from BiPN (73.7% prediction), whereas of the 34 patients with a  $< 3$ -fold increase, 23 experienced BiPN (67.6% prediction). Therefore, we concluded that pretreatment of phytohemagglutinin-induced IL2 mRNA levels in whole blood serve as a promising biomarker for predicting BiPN, and this finding warrants validation in a larger study.

[964]

**TÍTULO / TITLE:** - Gracilaria edulis extract induces apoptosis and inhibits tumor in Ehrlich Ascites tumor cells in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Complement Altern Med. 2013 Nov 25;13(1):331.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1472-6882-13-331](#)

**AUTORES / AUTHORS:** - Patra S; Muthuraman MS

**RESUMEN / SUMMARY:** - BACKGROUND: Marine environment is inestimable for their chemical and biological diversity and therefore is an extraordinary resource for the discovery of new anticancer drugs. Recent development in elucidation of the mechanism and therapeutic action of natural products helped to evaluate for their potential activity. METHODS: We evaluated Gracilaria edulis J. Ag (Brown algae), for its antitumor potential against the Ehrlich ascites tumor (EAT) in vivo and in vitro. Cytotoxicity evaluation of Ethanol Extract of Gracilaria edulis (EEGE) using EAT cells showed significant activity. In vitro studies indicated that EEGE cytotoxicity to EAT cells is mediated through its ability to produce reactive oxygen species (ROS) and therefore decreasing intracellular glutathione (GSH) levels may be attributed to oxidative stress. RESULTS: Apoptotic parameters including Annexin-V positive cells, increased levels of DNA fragmentation and increased caspase-2, caspase-3 and caspase-9 activities indicated the mechanism might be by inducing apoptosis. Intraperitoneally administration of EEGE to EAT-bearing mice helped to increase the lifespan of the animals significantly inhibited tumor growth and increased survival of mice. Extensive hematology, biochemistry and histopathological analysis of liver and kidney indicated that daily doses of EEGE up to 300 mg/kg for 35 days are well tolerated and did not cause hematotoxicity nor renal or hepatotoxicity. CONCLUSION: Comprehensive antitumor analysis in animal model and in Ehrlich Ascites Tumor cells was done including biochemical, and pathological evaluations indicate antitumor activity of the extract and non toxic in vivo. It was evident that the mechanism explains the apoptotic activity of the algae extract.

[965]

**TÍTULO / TITLE:** - Isoliquiritigenin Induces Caspase-Dependent Apoptosis via Downregulation of HPV16 E6 Expression in Cervical Cancer Ca Ski Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Planta Med. 2013 Nov;79(17):1628-35. doi: 10.1055/s-0033-1350956. Epub 2013 Nov 8.

●● Enlace al texto completo (gratis o de pago) [1055/s-0033-1350956](#)

**AUTORES / AUTHORS:** - Hirchaud F; Hermetet F; Ablise M; Fauconnet S; Vuitton DA; Pretet JL; Mougín C

**INSTITUCIÓN / INSTITUTION:** - Univ. Franche-Comte, Besançon, France.

**RESUMEN / SUMMARY:** - Flavonoids have antitumoral properties and may be attractive candidates as anticancer therapy. Isoliquiritigenin which is a constituent of licorice (*Glycyrrhiza inflata*), a plant commonly used in traditional Uyghur medicine in Xinjiang, China, was studied for antiproliferative and apoptotic activity in human cervical cancer cells, Ca Ski, SiHa, HeLa, and C-33A. Its molecular mechanism of action was specifically examined in Ca Ski cells. Isoliquiritigenin decreased cell viability, induced cell accumulation in G2/M and morphological and biochemical features of apoptosis in the four cancer cell lines. In Ca Ski cells, isoliquiritigenin led to a downregulation of HPV16 E6 expression associated with an increase of p53 and p21 levels, enhanced expression of Bax and decreased expression of Bcl-2 and Bid proform triggering dissipation of the mitochondrial membrane potential, released cytochrome c to the cytosol followed by activation of caspase cascade with cleavage of caspase-9, caspase-3, and PARP. Caspase-8 was also cleaved. Moreover treatment with a pan-caspase inhibitor prevented apoptosis. As Ca Ski cells are representative of carcinoma naturally occurring in the cervix, our results suggest a potential benefit of isoliquiritigenin for cervical cancer prevention and treatment.

[966]

**TÍTULO / TITLE:** - Transcriptome analysis of glioma cells for the dynamic response to gamma-irradiation and dual regulation of apoptosis genes: a new insight into radiotherapy for glioblastomas.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cell Death Dis. 2013 Oct 31;4:e895. doi: 10.1038/cddis.2013.412.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.412](#)

**AUTORES / AUTHORS:** - Ma H; Rao L; Wang HL; Mao ZW; Lei RH; Yang ZY; Qing H; Deng YL

**INSTITUCIÓN / INSTITUTION:** - School of Life Science, Beijing Institute of Technology, Beijing 100081, China.

**RESUMEN / SUMMARY:** - Ionizing radiation (IR) is of clinical importance for glioblastoma therapy; however, the recurrence of glioma characterized by radiation resistance remains a therapeutic challenge. Research on irradiation-induced transcription in glioblastomas can contribute to the understanding of radioresistance mechanisms. In this study, by using the total mRNA sequencing (RNA-seq) analysis, we assayed the global gene expression in a human glioma cell line U251 MG at various time points after exposure to a growth arrest dose of gamma-rays. We identified 1656 genes with obvious changes at the transcriptional level in response to irradiation, and these genes were dynamically enriched in various biological processes or pathways, including cell cycle arrest, DNA replication, DNA repair and apoptosis. Interestingly, the results showed that cell death was not induced even many

proapoptotic molecules, including death receptor 5 (DR5) and caspases were activated after radiation. The RNA-seq data analysis further revealed that both proapoptosis and antiapoptosis genes were affected by irradiation. Namely, most proapoptosis genes were early continually responsive, whereas antiapoptosis genes were responsive at later stages. Moreover, HMGB1, HMGB2 and TOP2A involved in the positive regulation of DNA fragmentation during apoptosis showed early continual downregulation due to irradiation. Furthermore, targeting of the TRAIL/DR5 pathway after irradiation led to significant apoptotic cell death, accompanied by the recovered gene expression of HMGB1, HMGB2 and TOP2A. Taken together, these results revealed that inactivation of proapoptotic signaling molecules in the nucleus and late activation of antiapoptotic genes may contribute to the radioresistance of gliomas. Overall, this study provided novel insights into not only the underlying mechanisms of radioresistance in glioblastomas but also the screening of multiple targets for radiotherapy.

[967]

**TÍTULO / TITLE:** - Bis (3,5-diiodo-2,4,6-trihydroxyphenyl) squaraine photodynamic therapy induces in vivo tumor ablation by triggering cytochrome c dependent mitochondria mediated apoptosis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Photodiagnosis Photodyn Ther. 2013 Dec;10(4):510-7. doi: 10.1016/j.pdpdt.2013.04.005. Epub 2013 Jun 29.

●● Enlace al texto completo (gratis o de pago) [1016/j.pdpdt.2013.04.005](#)

**AUTORES / AUTHORS:** - Devi DG; Cibir TR; Abraham A

**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry, University of Kerala, Kariavattom, Thiruvananthapuram 695581, Kerala, India.

**RESUMEN / SUMMARY:** - BACKGROUND: Despite findings that photodynamic treatment with bis (3,5-diiodo-2,4,6-trihydroxyphenyl) squaraine initiated tumor regression in mice skin, queries regarding its mode of action - answers to which will be functional to design clinical trials on squaraine based photodynamic therapy - remain unanswered. Our investigation reveals the in vivo mechanism of action of the photosensitizer. METHODS: Skin tumor was induced in Swiss albino mice using 7,12-dimethyl benzanthracene. After the intraperitoneal administration of the dye in tumor induced mice, its concentration in subcellular fractions of the tumor tissue was determined fluorimetrically. Cytochrome c release from the mitochondrial membrane after the photodynamic treatment was analyzed. The observations stemming from this part lead to histopathological examination of tumor tissues. Apoptotic markers like caspase-3, Bcl-2 and Bax were also studied. RESULTS: Major portion of the dye accumulated in the mitochondria. Cytochrome c leakage from mitochondria after squaraine PDT suggests loss of mitochondrial membrane integrity, which was further confirmed by the results of histopathological analysis. The activity of caspase-3 was elevated, expression of Bcl-2 diminished and that of Bax increased - all these results show enhancement of apoptosis in the tumor region after the treatment.

CONCLUSIONS: The results lead to the elucidation of mechanism of tumor destruction which proves to be mitochondria mediated apoptotic damage of tumor tissue. The study assumes significance since it defines the in vivo mode of action of a photosensitizer. Also, the query of how a squaraine based photosensitizer evokes tumor response is being dealt with here, for the first time.

[968]

**TÍTULO / TITLE:** - Selenium-binding protein 1 as a tumor suppressor and a prognostic indicator of clinical outcome.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Biomark Res. 2013 Dec 1;1(1):15.

●● Enlace al texto completo (gratis o de pago) [1186/2050-7771-1-15](#)

**AUTORES / AUTHORS:** - Yang W; Diamond AM

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, School of Basic Medical Sciences, Xinxiang Medical University, 601 East Jinsui Dadao, Xinxiang 453003, China ; Department of Pathology, University of Illinois at Chicago, Chicago, Illinois 60612, USA.

**RESUMEN / SUMMARY:** - Selenium is a trace element that plays a critical role in physiological processes and cancer prevention, whose functions may be through its effects on selenium-containing proteins. Selenium-binding protein 1 (SBP1) is a member of an unusual class of selenium-containing proteins that may function as a tumor suppressor in multiple cancer types and whose levels have been shown to be lower in cancers as compared to corresponding normal tissues. This review is intended to summarize recent advances in gaining an understanding of the significance of SBP1 in carcinogenesis, and suggest that SBP1 could be developed as a potential biomarker for cancer progression and prognosis.

[969]

**TÍTULO / TITLE:** - Extracellular signal-regulated kinase inhibition is required for methanol extract of Smilax china L. induced apoptosis through death receptor 5 in human oral mucocarcinoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Nov 22. doi: 10.3892/mmr.2013.1826.

●● Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1826](#)

**AUTORES / AUTHORS:** - Yu HJ; Shin JA; Lee SO; Kwon KH; Cho SD

**INSTITUCIÓN / INSTITUTION:** - Department of Oral Pathology, School of Dentistry and Institute of Oral Bioscience, Chonbuk National University, Jeonju, North Jeolla 561756, Republic of Korea.

**RESUMEN / SUMMARY:** - Smilax china L., a well-known Chinese traditional medicine, has been used as an anti-inflammatory, anticancer and analgesic agent, but its role has not yet been fully elucidated in oral mucocarcinoma (MEC). The present study focused on addressing the anticancer activity and molecular mechanism of methanol extract of Smilax china L. (MESC) in MC3 human oral MEC cells. The results indicated that MESC inhibited cell growth and induced apoptosis in MC3 cells. These observations were found to correlate with increases in truncated BH3 interacting domain death agonist and B-cell lymphoma 2 (Bcl2) interacting mediator of cell death, but not Bcl2 homologous antagonist killer, Bcl2-associated X protein, Bcl2, B-cell lymphoma extra large and induced myeloid leukemia cell differentiation protein levels. MESC also damaged the mitochondrial membrane potential, cleaved caspase-8 protein and increased death receptor 5 (DR5) protein levels by enhancing the stability of DR5 protein. Furthermore, MESC affected the phosphorylation of extracellular signal-regulated kinase (ERK) only, and did not affect c-Jun N-terminal kinase or p38 phosphorylation. Cotreatment with MESC and an ERK inhibitor (PD98059) significantly

increased the expression of DR5 to induce apoptosis in MC3 cells. Therefore, these results suggest that MESC may induce apoptosis via the ERK pathway and may be a potential anticancer drug candidate against human oral MEC.

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[970]

**TÍTULO / TITLE:** - Prognostic Importance and Therapeutic Implications of PAK1, a Drugable Protein Kinase, in Gastroesophageal Junction Adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 13;8(11):e80665. doi: 10.1371/journal.pone.0080665.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0080665](#)

**AUTORES / AUTHORS:** - Li Z; Zou X; Xie L; Dong H; Chen Y; Liu Q; Wu X; Zhou D; Tan D; Zhang H

**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 is a lethal cancer with rising incidence, yet the molecular biomarkers that have strong prognostic impact and also hold great therapeutic promise remain elusive. We used a data mining approach and identified the p21 protein-activated kinase 1 (PAK1), an oncogene and drugable protein kinase, to be among the most promising targets for GEJ adenocarcinoma. Immunoblot analysis and data mining demonstrated that PAK1 protein and mRNA were upregulated in cancer tissues compared to the noncancerous tissues. Immunohistochemistry revealed PAK1 overexpression in 72.6% of primary GEJ adenocarcinomas (n = 113). A step-wise increase in PAK1 levels was noted from paired normal epithelium, to atypical hyperplasia and adenocarcinoma. PAK1 overexpression in tumor was associated with lymph node (LN) metastasis (P<0.001), advanced tumor stage (P<0.001), large tumor size (P = 0.006), residual surgical margin (P = 0.033), and unfavorable overall survival (P<0.001). Multivariate analysis showed PAK1 overexpression is an independent high-risk prognostic predictor (P<0.001). Collectively, PAK1 is overexpressed during tumorigenic progression and its upregulation correlates with malignant properties mainly relevant to invasion and metastasis. PAK1 expression could serve as a prognostic predictor that holds therapeutic promise for GEJ adenocarcinoma.

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[971]

**TÍTULO / TITLE:** - Anti-proliferation Effects of Interferon-gamma on Gastric Cancer Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):5513-8.

**AUTORES / AUTHORS:** - Zhao YH; Wang T; Yu GF; Zhuang DM; Zhang Z; Zhang HX; Zhao DP; Yu AL

**INSTITUCIÓN / INSTITUTION:** - Institute of Aetiology, Department of Aetiology, Taishan Medical University, Taian, Shandong, China E-mail : [alyu@tsmc.edu.cn](mailto:alyu@tsmc.edu.cn), [yhzhao@tsmc.edu.cn](mailto:yhzhao@tsmc.edu.cn).

**RESUMEN / SUMMARY:** - IFN-gamma plays an indirect anti-cancer role through the immune system but may have direct negative effects on cancer cells. It regulates the viability of gastric cancer cells, so we examined whether it affects their proliferation and

how that might be brought about. We exposed AGS, HGC-27 and GES-1 gastric cancer cell lines to IFN-gamma and found significantly reduced colony formation ability. Flow cytometry revealed no effect of IFN-gamma on apoptosis of cell lines and no effect on cell aging as assessed by beta-gal staining. Microarray assay revealed that IFN-gamma changed the mRNA expression of genes related to the cell cycle and cell proliferation and migration, as well as chemokines and chemokine receptors, and immunity-related genes. Finally, flow cytometry revealed that IFN-gamma arrested the cells in the G1/S phase. IFN-gamma may slow proliferation of some gastric cancer cells by affecting the cell cycle to play a negative role in the development of gastric cancer.

[972]

**TÍTULO / TITLE:** - The advantage of circulating tumor cells over serum carcinoembryonic antigen for predicting treatment responses in rectal cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Future Oncol. 2013 Oct;9(10):1489-500. doi: 10.2217/fon.13.91.

●● Enlace al texto completo (gratis o de pago) [2217/fon.13.91](#)

**AUTORES / AUTHORS:** - Sun W; Huang T; Li G; Shen W; Zhu J; Jin Q; Zhao J; Jia C; Zhang Z

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Fudan University Shanghai Cancer Center, No. 270, Dong'an Road, Shanghai 200032, China.

**RESUMEN / SUMMARY:** - AIM: The objective of this study was to investigate the clinical significance of circulating tumor cells (CTCs) on the evaluation and prediction of treatment responses in rectal cancer patients compared with serum carcinoembryonic antigen (CEA). MATERIALS & METHODS: Both CTCs and CEA levels of 103 rectal cancer patients (66 with stage II-III and 37 with recurrence or metastasis) were analyzed before and after chemoradiotherapy. CTCs were detected using EpCAM magnetic bead-based enrichment combined with cytometric identification. RESULTS: CTCs were detected in all patients while no tumor cells were found in healthy controls. CTC levels in metastatic patients were significantly higher than those with recurrence or stage II-III rectal cancer. There is a close relationship between CTC levels and treatment outcomes but serum CEA did not have any correlation. CONCLUSION: CTCs are promising markers for the evaluation and prediction of treatment responses in rectal cancer patients, superior to the conventional tumor marker CEA.

[973]

**TÍTULO / TITLE:** - Chloroquine and valproic acid combined treatment in vitro has enhanced cytotoxicity in an osteosarcoma cell line.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(8):4651-4.

**AUTORES / AUTHORS:** - Wang CK; Yu XD; Li Q; Xie G; Teng Y

**INSTITUCIÓN / INSTITUTION:** - Department of Orthopaedics, The Fourth Hospital of Harbin, Harbin, Heilongjiang, China E-mail : [Wangchuankun05@163.com](mailto:Wangchuankun05@163.com).

**RESUMEN / SUMMARY:** - Chloroquine (CQ) and valproic acid (VPA) have been extensively studied for biological effects. Here, we focused on efficacy of combined CQ and VPA on osteosarcoma cell lines. Viability of osteosarcoma cell lines (U2OS and

HOS) was analyzed by MTT assay. Apoptotic assays and colony formation assays were also applied. ROS generation and Western Blotting were performed to determine the mechanism of CQ and VPA combination in the process of apoptosis. The viability of different osteosarcoma cell lines significantly decreased after CQ and VPA combination treatment compared with either drug used alone, and apoptosis was increased significantly. ROS generation was triggered leading to expression of apoptosis related genes being increased and of anti-apoptotic related genes being decreased. From our data shown here, CQ and VPA combination treatment in vitro enhanced cytotoxicity to osteosarcoma cells.

[974]

**TÍTULO / TITLE:** - Somatostatin receptor subtypes 2 and 5 are associated with better survival in operable hepatitis B-related hepatocellular carcinoma following octreotide long-acting release treatment.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oncol Lett. 2013 Sep;6(3):821-828. Epub 2013 Jul 1.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ol.2013.1435](#)

**AUTORES / AUTHORS:** - Liu Y; Jiang L; Mu Y

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatric Surgery, National Center for Cardiovascular Disease and Fuwei Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, P.R. China.

**RESUMEN / SUMMARY:** - Liver resections for hepatocellular carcinoma (HCC) in cirrhotic livers are associated with early recurrence and poor survival. Somatostatin analogues (SSAs) have been reported to inhibit cell proliferation by interacting with specific somatostatin receptors (SSTRs) 2 and 5. The present study investigated whether SSTR expression in HCC was associated with the clinical outcome following octreotide long-acting release (LAR) treatment. Paired tumor and cirrhotic liver samples were obtained following a liver resection from 99 patients with stage I-II HCC and HBV-related cirrhosis. The expression of SSTR2 and 5 was assessed using quantitative (q)PCR and immunohistochemistry. The patients were classified into two groups, the high expression (n=47) and low expression (n=52) groups, based on the gene expression levels. The clinicopathological data and survival results of the two groups were compared. When compared with the surrounding cirrhotic tissue, the SSTR2 and 5 mRNA levels were significantly decreased in the HCC tissue. There were no significant differences between the groups with respect to the baseline characteristics. The tumor recurrence rate was significantly lower in the high expression group compared with that of the low expression group (63.83% vs. 82.69%; P=0.033). The 1-, 3- and 5-year disease-free and overall survival rates of the high expression group were 97, 89 and 71% and 98, 89 and 74%, respectively. The survival time of the members of the high expression group was longer compared with that of the low expression group. The multivariate analysis revealed that the TNM-7 stage and SSTR2 expression were independent prognostic factors for survival. In conclusion, SSTR mRNA expression correlated with survival in patients with early-stage hepatitis B virus (HBV)-related HCC who were treated with octreotide LAR following surgery. The inhibitory effects of SSAs on tumor growth may be mediated by SSTR expression.

[975]

**TÍTULO / TITLE:** - CRM1 Inhibition Sensitizes Drug Resistant Human Myeloma Cells to Topoisomerase II and Proteasome Inhibitors both In Vitro and Ex Vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Cancer. 2013 Sep 10;4(8):614-25. doi: 10.7150/jca.7080.

●● Enlace al texto completo (gratis o de pago) [7150/jca.7080](#)

**AUTORES / AUTHORS:** - Turner JG; Dawson J; Emmons MF; Cubitt CL; Kauffman M; Shacham S; Hazlehurst LA; Sullivan DM

**INSTITUCIÓN / INSTITUTION:** - 1. Department of Blood and Marrow Transplantation and Chemical Biology and Molecular Medicine Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida 33612.

**RESUMEN / SUMMARY:** - Multiple myeloma (MM) remains an incurable disease despite improved treatments, including lenalidomide/pomalidomide and bortezomib/carfilzomib based therapies and high-dose chemotherapy with autologous stem cell rescue. New drug targets are needed to further improve treatment outcomes. Nuclear export of macromolecules is misregulated in many cancers, including in hematological malignancies such as MM. CRM1 (chromosome maintenance protein-1) is a ubiquitous protein that exports large proteins (>40 kDa) from the nucleus to the cytoplasm. We found that small-molecule Selective Inhibitors of Nuclear Export (SINE) prevent CRM1-mediated export of p53 and topoisomerase IIalpha (topo IIalpha). SINE's CRM1-inhibiting activity was verified by nuclear-cytoplasmic fractionation and immunocytochemical staining of the CRM1 cargoes p53 and topo IIalpha in MM cells. We found that SINE molecules reduced cell viability and induced apoptosis when used as both single agents in the sub-micromolar range and when combined with doxorubicin, bortezomib, or carfilzomib but not lenalidomide, melphalan, or dexamethasone. In addition, CRM1 inhibition sensitized MM cell lines and patient myeloma cells to doxorubicin, bortezomib, and carfilzomib but did not affect peripheral blood mononuclear or non-myeloma bone marrow mononuclear cells as shown by cell viability and apoptosis assay. Drug resistance induced by co-culture of myeloma cells with bone marrow stroma cells was circumvented by the addition of SINE molecules. These results support the continued development of SINE for patients with MM.

[976]

**TÍTULO / TITLE:** - Expressions of CLDN1 and insulin-like growth factor 2 are associated with poor prognosis in stage N2 non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin Med J (Engl). 2013;126(19):3668-74.

**AUTORES / AUTHORS:** - Zhang ZF; Pei BX; Wang AL; Zhang LM; Sun BS; Jiang RC; Wang CL

**INSTITUCIÓN / INSTITUTION:** - Department of Lung Cancer, Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, China (Email: [zhangzhenfa1973@163.com](mailto:zhangzhenfa1973@163.com)).

**RESUMEN / SUMMARY:** - BACKGROUND: Patients with single station mediastinal lymph node (N2) non-small cell lung cancer (NSCLC) have a better prognosis than those with multilevel N2. The molecular factors which are involved in disease progression remain largely unknown. The purpose of this study was to investigate gene expression differences between single station and multilevel N2 NSCLC and to identify the crucial molecular factors which are associated with progress and prognosis of

stage N2 NSCLC. METHODS: Gene expression analysis was performed using Agilent 4x44K Whole Human Genome Oligo Microarray on 10 freshfrozen lymph node tissue samples from single station N2 and paired multilevel N2 NSCLC patients. Real-time reverse transcription (RT)-PCR was used to validate the differential expression of 14 genes selected by cDNA microarray of which four were confirmed. Immunohistochemical staining for these validated genes was performed on formalin-fixed, paraffinembedded tissue samples from 130 cases of stage N2 NSCLC arranged in a high-density tissue microarray. RESULTS: We identified a 14 gene expression signature by comparative analysis of gene expression. Expression of these genes strongly differed between single station and multilevel N2 NSCLC. Four genes (ADAM28, MUC4, CLDN1, and IGF2) correlated with the results of microarray and real-time RT-PCR analysis for the gene-expression data in samples from 56 NSCLC patients. Immunohistochemical staining for these genes in samples from 130 cases of stage N2 NSCLC demonstrated the expression of IGF2 and CLDN1 was negatively correlated with overall survival of stage N2 NSCLC. CONCLUSIONS: Our results suggest that the expression of CLDN1 and IGF2 indicate a poor prognosis in stage N2 NSCLC. Further, CLDN1 and IGF2 may provide potential targeting opportunities in future therapies.

[977]

**TÍTULO / TITLE:** - Minnelide: a novel therapeutic that promotes apoptosis in non-small cell lung carcinoma in vivo.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Oct 15;8(10):e77411. doi: 10.1371/journal.pone.0077411.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0077411](#)

**AUTORES / AUTHORS:** - Rousalova I; Banerjee S; Sangwan V; Evenson K; McCauley JA; Kratzke R; Vickers SM; Saluja A; D'Cunha J

**INSTITUCIÓN / INSTITUTION:** - Division of Basic and Translational Research, Department of Surgery, University of Minnesota, Minneapolis, Minnesota, United States of America.

**RESUMEN / SUMMARY:** - BACKGROUND: Minnelide, a pro-drug of triptolide, has recently emerged as a potent anticancer agent. The precise mechanisms of its cytotoxic effects remain unclear. METHODS: Cell viability was studied using CCK8 assay. Cell proliferation was measured real-time on cultured cells using Electric Cell Substrate Impedance Sensing (ECIS). Apoptosis was assayed by Caspase activity on cultured lung cancer cells and TUNEL staining on tissue sections. Expression of pro-survival and anti-apoptotic genes (HSP70, BIRC5, BIRC4, BIRC2, UACA, APAF-1) was estimated by qRTPCR. Effect of Minnelide on proliferative cells in the tissue was estimated by Ki-67 staining of animal tissue sections. RESULTS: In this study, we investigated in vitro and in vivo antitumor effects of triptolide/Minnelide in non-small cell lung carcinoma (NSCLC). Triptolide/Minnelide exhibited anti-proliferative effects and induced apoptosis in NSCLC cell lines and NSCLC mouse models. Triptolide/Minnelide significantly down-regulated the expression of pro-survival and anti-apoptotic genes (HSP70, BIRC5, BIRC4, BIRC2, UACA) and up-regulated pro-apoptotic APAF-1 gene, in part, via attenuating the NF-kappaB signaling activity. CONCLUSION: In conclusion,

our results provide supporting mechanistic evidence for Minnelide as a potential in NSCLC.

[978]

**TÍTULO / TITLE:** - Zeaxanthin Induces Apoptosis in Human Uveal Melanoma Cells through Bcl-2 Family Proteins and Intrinsic Apoptosis Pathway.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Evid Based Complement Alternat Med. 2013;2013:205082. doi: 10.1155/2013/205082. Epub 2013 Oct 10.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/205082](#)

**AUTORES / AUTHORS:** - Bi MC; Rosen R; Zha RY; McCormick SA; Song E; Hu DN

**INSTITUCIÓN / INSTITUTION:** - Department of Ophthalmology, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, China.

**RESUMEN / SUMMARY:** - The cytotoxic effects of zeaxanthin on two human uveal melanoma cell lines (SP6.5 and C918) and related signaling pathways were studied and compared to effects on normal ocular cells (uveal melanocytes, retinal pigment epithelial cells, and scleral fibroblasts). MTT assay revealed that zeaxanthin reduced the cell viability of melanoma cells in a dose-dependent manner (10, 30, and 100  $\mu$ M), with IC<sub>50</sub> at 40.8 and 28.7  $\mu$ M in SP6.5 and C918 cell lines, respectively. Zeaxanthin did not affect the viability of normal ocular cells even at the highest levels tested (300  $\mu$ M), suggesting that zeaxanthin has a selectively cytotoxic effect on melanoma cells. Zeaxanthin induced apoptosis in melanoma cells as indicated by annexin V and ethidium III flow cytometry. Western blot analysis demonstrated that zeaxanthin decreased the expression of antiapoptotic proteins (Bcl-2 and Bcl-xL) and increased the expression of proapoptotic proteins (Bak and Bax) in zeaxanthin-treated melanoma cells. Zeaxanthin increased mitochondrial permeability as determined by JC-1 fluorescein study. Zeaxanthin also increased the level of cytosol cytochrome c and caspase-9 and -3 activities, but not caspase-8, as measured by ELISA assay or colorimetric assay. All of these findings indicate that the intrinsic (mitochondrial) pathway is involved in zeaxanthin-induced apoptosis in uveal melanoma cells.

[979]

**TÍTULO / TITLE:** - Hepatocellular carcinoma after sustained viral response to interferon and ribavirin therapy in cirrhosis secondary to chronic hepatitis C.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Coll Physicians Surg Pak. 2013 Oct;23(10):699-702. doi: 10.2013/JCPSP.699702.

●● [Enlace al texto completo \(gratis o de pago\) 2013/JCPSP.699702](#)

**AUTORES / AUTHORS:** - Khokhar N; Niazi TK; Qureshi MO

**INSTITUCIÓN / INSTITUTION:** - Department of Gastroenterology / Medicine, Shifa International Hospital, Islamabad.

**RESUMEN / SUMMARY:** - **OBJECTIVE:** To determine the frequency of development of hepatocellular carcinoma in patients with chronic liver disease secondary to hepatitis C who had achieved sustained virological response with Interferon and Ribavirin therapy. **STUDY DESIGN:** Retrospective descriptive study. **PLACE AND DURATION OF STUDY:** Shifa International Hospital, Islamabad, Pakistan, from January 2007 to January 2012. **METHODOLOGY:** Hepatitis C related chronic liver disease patients who were treated with interferon and ribavirin, after they achieved sustained virological

response, they were followed for a mean of 42 +/- 17 months. During this time, development of hepatocellular carcinoma was ascertained. All underwent surveillance with alpha-feto-protein and ultrasonography every 6 months. RESULTS: Out of the 58 patients who had achieved sustained virological response, 3 developed hepatocellular carcinoma after a mean follow-up of 38 +/- 14 months. It was multifocal in 2 cases and was single lesion in the 3<sup>rd</sup>. Two patients ultimately died, one with upper GI bleeding and the other with hepatic encephalopathy, while 3<sup>rd</sup> patient with single lesion is still surviving. CONCLUSION: Three out of 58 patients of hepatitis C related chronic liver disease developed hepatocellular carcinoma during follow-up in patients who had achieved sustained virological response. These patients need closer follow-up, for development of complications, even if they have achieved sustained viral response.

[980]

**TÍTULO / TITLE:** - Characteristics and Prognosis of Adult Acute Myeloid Leukemia with Internal Tandem Duplication in the FLT3 Gene.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Oman Med J. 2013 Nov;28(6):432-40. doi: 10.5001/omj.2013.121.

●● Enlace al texto completo (gratis o de pago) [5001/omj.2013.121](#)

**AUTORES / AUTHORS:** - Al-Mawali A; Gillis D; Lewis I

**INSTITUCIÓN / INSTITUTION:** - The Director, Directorate of Research and Studies, Directorate General of Planning, Ministry of Health, PO Box 393, PC 113, Muscat, Sultanate of Oman.

**RESUMEN / SUMMARY:** - OBJECTIVES: Constitutive activation of the fms-like tyrosine kinase 3 (FLT3) receptor by internal tandem duplication (ITD) of the juxtamembrane region has been described in patients with acute myeloid leukemia. FLT3/ITDs are present in about 20-30% of all acute myeloid leukemia cases. It has been shown that the mutation is correlated with worse prognosis. However, none of the previous studies investigated which FAB subtype is associated with higher percentage of FLT3/ITD, thus the reason for undertaking the current study. METHODS: The prevalence and the potential prognostic impact of FLT3 mutations in 39 acute myeloid leukemia patients were analyzed by genomic polymerase chain reaction. Twelve samples with FLT3/ITDs and 27 acute myeloid leukemia samples without the mutations were compared with respect to clinical prognosis and FAB subtype. Results were correlated with cytogenetic data and the clinical response. RESULTS: FLT3/ITD mutations were found in 31% of patients. FLT3/ITD was associated with similar clinical characteristics and was more prevalent in patients with normal karyotype (83%). Interestingly, half of the FLT3/ITD aberrations were found in patients with FAB M1 (50%), and fewer were found in patients with FAB M2 (8%), M4 (8%), and M5 (8%). Although less frequent in patients with cytogenetic aberrations, FLT3/ITDs were found in 17% of patients with t(15;17). Although the study was powered to 80%, patients with FLT3/ITD mutation did not show shorter complete remission duration or a higher relapse rate. CONCLUSION: The data confirm that FLT3/ITD mutations represent a common alteration in adult acute myeloid leukemia, mainly with normal karyotype (83%) and de novo acute myeloid leukemia (75%), as compared to secondary acute myeloid leukemia (25%) (p<0.001). It also showed that half of the M1-FAB subtype is FLT3/ITD positive. Therefore,

FLT3/ITD is a therapeutic target, and thus inhibition of FLT3 tyrosine kinase activity may provide a new approach in the treatment of leukemia carrying these mutations.

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[981]

**TÍTULO / TITLE:** - Hypoxia- and radiation-induced overexpression of Smac by an adenoviral vector and its effects on cell cycle and apoptosis in MDA-MB-231 human breast cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Ther Med. 2013 Dec;6(6):1560-1564. Epub 2013 Oct 16.

●● [Enlace al texto completo \(gratis o de pago\) 3892/etm.2013.1351](#)

**AUTORES / AUTHORS:** - Liu WW; Liu Y; Liang S; Wu JH; Wang ZC; Gong SL

**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Radiobiology, Ministry of Health, School of Public Health, Jilin University, Changchun, Jilin 130021, P.R. China ; Department of Radiology, Second Hospital, Jilin University, Changchun, Jilin 130041, P.R. China.

**RESUMEN / SUMMARY:** - A conditionally replicative adenoviral (CRAd) vector, designated as CRAd.pEgr-1-Smac, that promotes the overexpression of second mitochondria-derived activator of caspase (Smac) when stimulated by hypoxia and radiation was constructed. MDA-MB-231 cells were transfected with CRAd.pEgr-1-Smac and treated with 4-Gy X-rays. The hypoxic status in cancer cells was mimicked with the chemical reagent CoCl<sub>2</sub>. Smac protein expression was measured by a western blotting assay and cell proliferation was detected with the MTT assay. The cell cycle progression and apoptotic percentage were measured by flow cytometry with PI and Annexin V-FITC staining kits, respectively, following the irradiation of the transfected cells with 4-Gy X-rays. The results showed that CRAd.pEgr-1-Smac was able to increase the Smac protein expression induced by hypoxia and radiation, inhibit cell proliferation and promote apoptosis. Therefore, this method of gene-radiotherapy is indicated to be an ideal strategy for the treatment of breast cancer.

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[982]

**TÍTULO / TITLE:** - Using protein interaction database and support vector machines to improve gene signatures for prediction of breast cancer recurrence.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Med Signals Sens. 2013 Apr;3(2):87-93.

**AUTORES / AUTHORS:** - Sehhati MR; Dehnavi AM; Rabbani H; Javanmard SH

**INSTITUCIÓN / INSTITUTION:** - Department of Biomedical Engineering, Isfahan University of Medical Sciences, Isfahan, Iran.

**RESUMEN / SUMMARY:** - Numerous studies used microarray gene expression data to extract metastasis-driving gene signatures for the prediction of breast cancer relapse. However, the accuracy and generality of the previously introduced biomarkers are not acceptable for reliable usage in independent datasets. This inadequacy is attributed to ignoring gene interactions by simple feature selection methods, due to their computational burden. In this study, an integrated approach with low computational cost was proposed for identifying a more predictive gene signature, for prediction of breast cancer recurrence. First, a small set of genes was primarily selected as signature by an appropriate filter feature selection (FFS) method. Then, a binary subclass of protein-protein interaction (PPI) network was used to expand the primary set by adding adjacent proteins of each gene signature from the PPI-network.

Subsequently, the support vector machine-based recursive feature elimination (SVMRFE) method was applied to the expression level of all the genes in the expanded set. Finally, the genes with the highest score by SVMRFE were selected as the new biomarkers. Accuracy of the final selected biomarkers was evaluated to classify four datasets on breast cancer patients, including 800 cases, into two cohorts of poor and good prognosis. The results of the five-fold cross validation test, using the support vector machine as a classifier, showed more than 13% improvement in the average accuracy, after modifying the primary selected signatures. Moreover, the method used in this study showed a lower computational cost compared to the other PPI-based methods. The proposed method demonstrated more robust and accurate biomarkers using the PPI network, at a low computational cost. This approach could be used as a supplementary procedure in microarray studies after applying various gene selection methods.

[983]

**TÍTULO / TITLE:** - Role of apoptosis in colon cancer biology, therapy, and prevention.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Curr Colorectal Cancer Rep. 2013 Dec;9(4). doi: 10.1007/s11888-013-0188-z.

●● Enlace al texto completo (gratis o de pago) [1007/s11888-013-0188-z](#)

**AUTORES / AUTHORS:** - Zhang L; Yu J

**INSTITUCIÓN / INSTITUTION:** - University of Pittsburgh Cancer Institute Pittsburgh, PA, 15213 ; Department of Pharmacology & Chemical Biology University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213.

**RESUMEN / SUMMARY:** - Deregulation of apoptosis is a hallmark of human cancer and contributes to therapeutic resistance. Recent advances in cancer genomics reveal a myriad of alterations in key pathways that directly or indirectly increase tumor cell survival. This review will outline the pathways of apoptosis in mammalian cells, and highlight the common alterations of apoptosis regulators found in colon cancer, the role of apoptosis and underlying mechanisms in colon cancer treatment and prevention, including recent advances on investigational agents, such as kinase inhibitors, proteasome inhibitors, HSP90 inhibitors, BH3 mimetics, TRAIL, and IAP antagonists. Topics will also include novel concepts, as well as opportunities and challenges for drug discovery and combination therapy by exploring cancer-specific genetic defects, and therefore selective induction of apoptosis in cancer cells. Although the emphasis is on colon cancer, the main theme and many of the aspects are applicable to other solid tumors.

[984]

**TÍTULO / TITLE:** - Hierarchy of gene expression data is predictive of future breast cancer outcome.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Phys Biol. 2013 Oct;10(5):056006. doi: 10.1088/1478-3975/10/5/056006. Epub 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [1088/1478-3975/10/5/056006](#)

**AUTORES / AUTHORS:** - Chen M; Deem MW

**INSTITUCIÓN / INSTITUTION:** - Department of Physics and Astronomy, Rice University, Houston, TX 77005, USA.

**RESUMEN / SUMMARY:** - We calculate measures of hierarchy in gene and tissue networks of breast cancer patients. We find that the likelihood of metastasis in the future is correlated with increased values of network hierarchy for expression networks of cancer-associated genes, due to the correlated expression of cancer-specific pathways. Conversely, future metastasis and quick relapse times are negatively correlated with the values of network hierarchy in the expression network of all genes, due to the dedifferentiation of gene pathways and circuits. These results suggest that the hierarchy of gene expression may be useful as an additional biomarker for breast cancer prognosis.

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[985]

**TÍTULO / TITLE:** - Pre-clinical evaluation of tyrosine kinase inhibitors for treatment of acute leukemia.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Vis Exp. 2013 Sep 18;(79):e50720. doi: 10.3791/50720.

●● Enlace al texto completo (gratis o de pago) [3791/50720](#)

**AUTORES / AUTHORS:** - Christoph S; Lee-Sherick AB; Sather S; DeRyckere D; Graham DK

**INSTITUCIÓN / INSTITUTION:** - Department of Pediatrics, University of Colorado Anschutz Medical Campus.

**RESUMEN / SUMMARY:** - Receptor tyrosine kinases have been implicated in the development and progression of many cancers, including both leukemia and solid tumors, and are attractive druggable therapeutic targets. Here we describe an efficient four-step strategy for pre-clinical evaluation of tyrosine kinase inhibitors (TKIs) in the treatment of acute leukemia. Initially, western blot analysis is used to confirm target inhibition in cultured leukemia cells. Functional activity is then evaluated using clonogenic assays in methylcellulose or soft agar cultures. Experimental compounds that demonstrate activity in cell culture assays are evaluated in vivo using NOD-SCID-gamma (NSG) mice transplanted orthotopically with human leukemia cell lines. Initial in vivo pharmacodynamic studies evaluate target inhibition in leukemic blasts isolated from the bone marrow. This approach is used to determine the dose and schedule of administration required for effective target inhibition. Subsequent studies evaluate the efficacy of the TKIs in vivo using luciferase expressing leukemia cells, thereby allowing for non-invasive bioluminescent monitoring of leukemia burden and assessment of therapeutic response using an in vivo bioluminescence imaging system. This strategy has been effective for evaluation of TKIs in vitro and in vivo and can be applied for identification of molecularly-targeted agents with therapeutic potential or for direct comparison and prioritization of multiple compounds.

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[986]

**TÍTULO / TITLE:** - The interleukin-6-type cytokine oncostatin M induces aryl hydrocarbon receptor expression in a STAT3-dependent manner in human HepG2 hepatoma cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - FEBS J. 2013 Oct 16. doi: 10.1111/febs.12571.

●● Enlace al texto completo (gratis o de pago) [1111/febs.12571](#)

**AUTORES / AUTHORS:** - Stobbe-Maicherski N; Wolff S; Wolff C; Abel J; Sydlík U; Frauenstein K; Haarmann-Stemmann T

**INSTITUCIÓN / INSTITUTION:** - IUF - Leibniz Research Institute for Environmental Medicine, Duesseldorf, Germany.

**RESUMEN / SUMMARY:** - The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor that mediates the toxicity of dioxins, polycyclic aromatic hydrocarbons and related environmental pollutants. Besides drug metabolism, several studies have provided evidence that the AHR and its downstream targets trigger important developmental, physiological and pathophysiological processes. However, in contrast to the molecular mechanisms of AHR-dependent signaling pathways, the transcriptional regulation of the AHR gene itself is as yet only marginally understood. We found that the pleiotropic interleukin (IL)-6-type cytokine oncostatin M (OSM) is an inducer of AHR mRNA and protein expression in human HepG2 hepatocarcinoma cells. Analyses of the human AHR promoter revealed the existence of a putative signal transducer and activator of transcription (STAT)-binding element 5'-upstream of the transcription start site. By means of site-directed mutagenesis, inhibitor experiments and electrophoretic mobility shift assays, we demonstrated that this STAT motif is recognized by STAT3 to regulate basal and cytokine-inducible AHR expression in HepG2 cells. The identification of the AHR as a downstream target of IL-6-type cytokine-stimulated STAT3 signaling may contribute to a better understanding of the multiple facets of AHR during development, physiology and disease.

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[987]

**TÍTULO / TITLE:** - Identification of the IGF1/PI3K/NFkB/ERK gene signalling networks associated with chemotherapy resistance and treatment response in high-grade serous epithelial ovarian cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Cancer. 2013 Nov 16;13(1):549.

- Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-549](#)

**AUTORES / AUTHORS:** - Koti M; Gooding RJ; Nuin P; Haslehurst A; Crane C; Weberpals J; Childs T; Bryson P; Dharsee M; Evans K; Feilotter HE; Park PC; Squire JA

**RESUMEN / SUMMARY:** - BACKGROUND: Resistance to platinum-based chemotherapy remains a major impediment in the treatment of serous epithelial ovarian cancer. The objective of this study was to use gene expression profiling to delineate major deregulated pathways and biomarkers associated with the development of intrinsic chemotherapy resistance upon exposure to standard first-line therapy for ovarian cancer. METHODS: The study cohort comprised 28 patients divided into two groups based on their varying sensitivity to first-line chemotherapy using progression free survival (PFS) as a surrogate of response. All 28 patients had advanced stage, high-grade serous ovarian cancer, and were treated with standard platinum-based chemotherapy. Twelve patient tumours demonstrating relative resistance to platinum chemotherapy corresponding to shorter PFS (< eight months) were compared to sixteen tumours from platinum-sensitive patients (PFS > eighteen months). Whole transcriptome profiling was performed using a Affymetrix high-resolution microarray platform to permit global comparisons of gene expression profiles between tumours from the resistant group and the sensitive group. RESULTS: Microarray data analysis revealed a set of 204 discriminating genes possessing expression levels which could influence differential chemotherapy response between the two groups. Robust statistical testing was then performed which eliminated a dependence on the

normalization algorithm employed, producing a restricted list of differentially regulated genes, and which found IGF1 to be the most strongly differentially expressed gene. Pathway analysis, based on the list of 204 genes, revealed enrichment in genes primarily involved in the IGF1/PI3K/NFkB/ERK gene signalling networks. CONCLUSIONS: This study has identified pathway specific prognostic biomarkers possibly underlying a differential chemotherapy response in patients undergoing standard platinum-based treatment of serous epithelial ovarian cancer. In addition, our results provide a pathway context for further experimental validations, and the findings are a significant step towards future therapeutic interventions.

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[988]

**TÍTULO / TITLE:** - Effects of metallothionein-3 and metallothionein-1E gene transfection on proliferation, cell cycle, and apoptosis of esophageal cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Genet Mol Res. 2013 Oct 17;12(4):4595-603. doi: 10.4238/2013.October.17.2.

●● [Enlace al texto completo \(gratis o de pago\) 4238/2013.October.17.2](#)

**AUTORES / AUTHORS:** - Tian ZQ; Xu YZ; Zhang YF; Ma GF; He M; Wang GY

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China.

**RESUMEN / SUMMARY:** - Metallothionein (MT)-3 has cell growth inhibitory activity, and is the only currently known MT subtype with unique physiological functions. The expression levels of MT-1E, a subtype of MT-1, were positively correlated with the degree of esophageal cancer malignancy. The present study aimed to investigate the effects of MT-3 and MT-1E gene transfection on the proliferation, cell cycle, and apoptosis of esophageal cancer cells. The cationic liposome method was used to transfect the esophageal cancer strains Eca-109 and TE13. Reverse transcription-polymerase chain reaction was used to detect target gene expression, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction was applied to detect cell proliferation, and flow cytometry was used for cell cycle and apoptosis detection. Esophageal cancer cells with MT-3 and MT-1E gene transfection showed high expression of the foreign target gene and mRNA. Cells with MT-3 gene transfection showed markedly inhibited proliferation ( $P < 0.05$ ), a significantly higher proportion of cells in the G0/G1 phase ( $P < 0.05$ ), a significantly lower proportion of cells in the S phase ( $P < 0.05$ ), and a significantly increased apoptosis rate ( $P < 0.05$ ). Cells with MT-1E gene transfection did not show significant changes in proliferation, cell cycle, or apoptosis rate ( $P > 0.05$ ). Therefore, the upregulation of MT-3 gene expression can inhibit esophageal cancer cell proliferation and induce apoptosis, which may be achieved by blocking the tumor cell growth cycle, whereas effects of the MT-1E gene on the proliferation of esophageal cancer cells were not evident.

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[989]

**TÍTULO / TITLE:** - The prognostic value of ERCC1 and RRM1 gene expression in completely resected non-small cell lung cancer: tumor recurrence and overall survival.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Cancer Manag Res. 2013 Oct 3;5:327-36. doi: 10.2147/CMAR.S52073.

●● [Enlace al texto completo \(gratis o de pago\) 2147/CMAR.S52073](#)

**AUTORES / AUTHORS:** - Tantraworasin A; Saeteng S; Lertprasertsuke N; Arayawudhikul N; Kasemsarn C; Patumanond J

**INSTITUCIÓN / INSTITUTION:** - General Thoracic Unit, Department of Surgery, Faculty of Medicine, Chiang Mai University Hospital, Chiang Mai, Thailand.

**RESUMEN / SUMMARY:** - **BACKGROUND:** The roles of excision repair cross-complementing group 1 gene (ERCC1) expression and ribonucleotide reductase subunit M1 gene (RRM1) expression in completely resected non-small cell lung cancer (NSCLC) are still debatable. Previous studies have shown that both genes affected the overall survival and outcomes of patients who received platinum-based chemotherapy; however, some studies did not show this correlation. The aim of this study was to evaluate the prognostic values of ERCC1 and RRM1 gene expression in predicting tumor recurrence and overall survival in patients with completely resected NSCLC who received adjuvant chemotherapy and in those who did not. **PATIENTS AND METHODS:** A retrospective cohort study was conducted in 247 patients with completely resected NSCLC. All patients had been treated with anatomic resection (lobectomy or pneumonectomy) with systematic mediastinal lymphadenectomy between January 2002 and December 2011 at Chiang Mai University Hospital, Chiang Mai, Thailand. They were divided into two groups: recurrence and no recurrence. Protein expression of ERCC1 and RRM1 was determined by immunohistochemistry. Correlations between clinicopathologic variables, including ERCC1 and RRM1 expression and tumor recurrence, were analyzed. Univariate and multivariate Cox proportional hazards regression analysis stratified by nodal involvement, tumor staging, intratumoral blood vessel invasion, intratumoral lymphatic invasion, and tumor necrosis was used to identify the prognostic roles of ERCC1 and RRM1. **RESULTS:** ERCC1 and RRM1 expression did not demonstrate prognostic value for tumor recurrence and overall survival in patients with completely resected NSCLC. In patients who did not receive adjuvant chemotherapy treatment, those with high ERCC1 and high RRM1 expression seemed to have greater potential for tumor recurrence and shorter overall survival than did those who had low ERCC1 and low RRM1 (hazard ratio [HR] =1.7, 95% confidence interval [CI] =0.6-4.3, P=0.292 and HR =1.6, 95% CI =0.5-4.5, P=0.411, respectively). In contrast, in patients who received adjuvant chemotherapy treatment, those with high ERCC1 and high RRM1 expression seemed to have benefited from adjuvant chemotherapy and showed good overall survival compared with those who had low ERCC1 and low RRM1 (HR =0.8, 95% CI = 0.4-1.8, P=0.612 and HR = 0.4, 95% CI = 0.1-2.4, P=0.325, respectively). Subgroup analysis in patients whose first-line metastatic chemotherapy failed demonstrated that ERCC1 expression and RRM1 expression were not prognostic factors for tumor recurrence and overall survival; however, patients who had high ERCC1 and high RRM1 expression seemed to have benefited from first-line chemotherapy treatment (HR =0.7, 95% CI =0.3-1.8, P=0.458). **CONCLUSION:** ERCC1 expression and RRM1 expression were not prognostic of tumor recurrence and overall survival in patients with completely resected NSCLC, either with or without adjuvant chemotherapy. Prospective studies that include a larger number of patients are needed for definite conclusions.

[990]

**TÍTULO / TITLE:** - Induction of apoptosis by sarijang, a bamboo salt sauce, in U937 human leukemia cells through the activation of caspases.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Exp Ther Med. 2013 Aug;6(2):381-387. Epub 2013 Jun 10.

●● Enlace al texto completo (gratis o de pago) [3892/etm.2013.1151](http://3892/etm.2013.1151)

**AUTORES / AUTHORS:** - Choi EA; Park C; Han MH; Lee JH; Kim GY; Choi BT; Choi YH

**INSTITUCIÓN / INSTITUTION:** - Insan Bamboo Salt Inc. and Insan Oriental Medical Clinic, Hamyang, Gyeongsangnam-do 676-805;

**RESUMEN / SUMMARY:** - Sarijang is a bamboo salt soy sauce, containing extracts of *Rhynchosia nulubilis*, sulfur-fed duck, dried bark of *Ulmus davidiana* and *Allium sativum*, which has been demonstrated to exert anti-inflammatory and antitumor activity. However, the cellular and molecular mechanisms of action of sarijang have not yet been elucidated. In the present study, we investigated the pro-apoptotic effects of sarijang in an in vitro U937 human leukemia cell model. Treatment with sarijang resulted in a concentration-dependent growth inhibition of the cells, coupled with the characteristic morphological features of apoptosis. The induction of the apoptotic cell death of the U937 cells by sarijang exhibited a correlation with the upregulation of death receptor 4 (DR4), the downregulation of members of the inhibitor of apoptosis protein (IAP) family, including survivin and cellular IAP (cIAP)-1, and the cleavage of Bid. Apoptosis-inducing concentrations of sarijang also induced the activation of caspases (caspase-3, -8 and -9), accompanied by proteolytic degradation of poly(ADP-ribose)-polymerase, beta-catenin and phospholipase C-gamma1. However, the apoptosis induced by sarijang was significantly inhibited by z-VED-fmk, a pan-caspase inhibitor, which demonstrated the importance of caspases in the process. These results suggested that sarijang may be a potential chemotherapeutic agent for use in the control of U937 human leukemia cells. Further studies are required to identify the active compounds in sarijang.

[991]

**TÍTULO / TITLE:** - Rhizoctonia Bataticola Lectin (RBL) Induces Caspase-8-Mediated Apoptosis in Human T-Cell Leukemia Cell Lines but Not in Normal CD3 and CD34 Positive Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Nov 14;8(11):e79311. doi: 10.1371/journal.pone.0079311.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0079311](http://1371/journal.pone.0079311)

**AUTORES / AUTHORS:** - Pujari R; Eligar SM; Kumar N; Barkeer S; Reddy V; Swamy BM; Inamdar SR; Shastry P

**INSTITUCIÓN / INSTITUTION:** - National Centre for Cell Science, Pune University Campus, Pune, Maharashtra, India.

**RESUMEN / SUMMARY:** - We have previously demonstrated immunostimulatory activity of a fungal lectin, *Rhizoctonia bataticola* lectin (RBL), towards normal human peripheral blood mononuclear cells. The present study aimed to explore the anticancer activities of RBL using human leukemic T-cell lines, Molt-4, Jurkat and HuT-78. RBL exhibited significant binding (>90%) to the cell membrane that was effectively inhibited by complex glycoproteins such as mucin (97% inhibition) and asialofetuin (94% inhibition) but not simple sugars such as N-acetyl-D-galactosamine, glucose and sucrose. RBL induced a dose and time dependent inhibition of proliferation and induced cytotoxicity in the cell lines. The percentage of apoptotic cells, as determined by hypodiploidy, was 33% and 42% in Molt-4 and Jurkat cells, respectively, compared to 3.11% and 2.92%

in controls. This effect was associated with a concomitant decrease in the G0/G1 population. Though initiator caspase-8 and -9 were activated upon exposure to RBL, inhibition of caspase-8 but not caspase-9 rescued cells from RBL-induced apoptosis. Mechanistic studies revealed that RBL induced cleavage of Bid, loss of mitochondrial membrane potential and activation of caspase-3. The expression of the anti-apoptotic proteins Bcl-2 and Bcl-X was down regulated without altering the expression of pro-apoptotic proteins- Bad and Bax. In contrast to leukemic cells, RBL did not induce apoptosis in normal PBMC, isolated CD3+ve cells and undifferentiated CD34+ve hematopoietic stem and progenitor cells (HSPCs). The findings highlight the differential effects of RBL on transformed and normal hematopoietic cells and suggest that RBL may be explored for therapeutic applications in leukemia.

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[992]

**TÍTULO / TITLE:** - Tempranillo-derived grape seed extract induces apoptotic cell death and cell growth arrest in human promyelocytic leukemia HL-60 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Food Funct. 2013 Dec 20;4(12):1759-66. doi: 10.1039/c3fo60267b. Epub 2013 Oct 16.

●● Enlace al texto completo (gratis o de pago) [1039/c3fo60267b](#)

**AUTORES / AUTHORS:** - Espino J; Gonzalez-Gomez D; Moreno D; Fernandez-Leon MF; Rodriguez AB; Pariente JA; Delgado-Adamez J

**INSTITUCIÓN / INSTITUTION:** - Department of Physiology, Neuroimmunophysiology and Chrononutrition Research Group, Faculty of Science, University of Extremadura, 06006 Badajoz, España. [jespino@unex.es](mailto:jespino@unex.es).

**RESUMEN / SUMMARY:** - Although grape seed extract (GSE) has proven to be effective against various cancers, few studies have investigated the effects of GSE on human leukemia. In this study, we analysed the mechanisms involved in the apoptotic effects induced by GSE on human promyelocytic leukemia HL-60 cells. Thus, GSE treatment succeeded in activating caspase-3 ( $P < 0.05$ ), the activation being dose-dependent and time-dependent. Activation of caspase-3 induced by GSE was accompanied by mitochondrial membrane depolarization ( $P < 0.05$ ). Moreover, disruption of mitochondrial integrity caused by GSE treatment subsequently led to activation of caspase-9 ( $P < 0.05$ ), and also produced a slight increase in ROS levels ( $P < 0.05$ ). Cytotoxic effects elicited by GSE treatment ultimately resulted in extensive S-phase arrest ( $P < 0.05$ ) and a substantial increase in the intrinsic rate of apoptosis ( $P < 0.05$ ). Our findings suggest that the GSE induces apoptotic cell death and cell growth inhibition in human leukemic HL-60 cells, which seems to be dependent on mitochondrial damage. Therefore, the GSE obtained from Tempranillo cultivars could be an effective approach to restrain uncontrolled cell proliferation and survival in leukemia cells.

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[993]

**TÍTULO / TITLE:** - Clerodane diterpenes isolated from *Polyalthia longifolia* induce apoptosis in human leukemia HL-60 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - J Oleo Sci. 2013;62(10):843-8.

**AUTORES / AUTHORS:** - Sari DP; Ninomiya M; Efdi M; Santoni A; Ibrahim S; Tanaka K; Koketsu M

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Andalas.

**RESUMEN / SUMMARY:** - Polyalthia is a versatile genus of shrubs and trees found in tropic and sub-tropic regions. In this study, three clerodane diterpenes, kolavenic acid (1), polyalthialdoic acid (2), and 16 $\alpha$ -hydroxy-cleroda-3,13(14)Z-dien-15,16-olide (3) isolated from Polyalthia longifolia leaves were evaluated for their apoptotic potential against human leukemia HL-60 cells. Compounds 2 and 3 inhibited cell proliferation with IC<sub>50</sub> values of 21.8 and 13.7  $\mu$ M, respectively. Morphological changes and DNA fragmentation analysis indicated that these diterpenes induce apoptotic cell death in the HL-60 cells. Our results revealed the importance of P. longifolia as a chemopreventive medicinal plant.

[994]

**TÍTULO / TITLE:** - Prognostic significance of serum carcinoembryonic antigen normalization on survival in rectal cancer treated with preoperative chemoradiation.

**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 Sep;45(3):186-92. doi:

10.4143/crt.2013.45.3.186. Epub 2013 Sep 30.

- Enlace al texto completo (gratuito o de pago) [4143/crt.2013.45.3.186](#)

**AUTORES / AUTHORS:** - Chung MJ; Chung SM; Kim JY; Ryu MR

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, The Catholic University of Korea, College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - **PURPOSE:** The purpose of this retrospective study was to identify factors predictive of survival in rectal cancer patients who received surgery with curative intent after preoperative chemoradiotherapy (CRT). **MATERIALS AND METHODS:** Between July 1996 and June 2010, 104 patients underwent surgery for rectal cancer after preoperative CRT. The median dose of radiotherapy was 50.4 Gy (range, 43.2 to 54.4 Gy) for 6 weeks. Chemotherapy was a bolus injection of 5-fluorouracil and leucovorin for the first and last week of radiotherapy (n=84, 77.1%) or capecitabine administered daily during radiotherapy (n=17, 16.3%). Low anterior resection (n=86, 82.7%) or abdominoperineal resection (n=18, 17.3%) was performed at a median 47 days from the end of radiotherapy, and four cycles of adjuvant chemotherapy was administered. The serum carcinoembryonic antigen (CEA) level was checked at initial diagnosis and just before surgery. **RESULTS:** After a median follow-up of 48 months (range, 9 to 174 months), 5-year disease free survival (DFS) was 74.5% and 5-year overall survival (OS) was 86.4%. Down staging of T diagnoses occurred in 32 patients (30.8%) and of N diagnoses in 40 patients (38.5%). The CEA change from initial diagnosis to pre-surgery (high-high vs. high-normal vs. normal-normal) was a statistically significant prognostic factor for DFS (p=0.012), OS (p=0.002), and distant metastasis free survival (p=0.018) in a multivariate analysis. **CONCLUSION:** Patients who achieve normal CEA level by the time of surgery have a more favorable outcome than those who retain a high CEA level after preoperative CRT. The normalization of CEA levels can provide important information about the prognosis in rectal cancer treatment.

[995]

**TÍTULO / TITLE:** - Targeted Silencing of Inhibitors of Apoptosis Proteins with siRNAs: A Potential Anti-cancer Strategy for Hepatocellular Carcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Asian Pac J Cancer Prev. 2013;14(9):4943-52.

**AUTORES / AUTHORS:** - Li G; Chang H; Zhai YP; Xu W

**INSTITUCIÓN / INSTITUTION:** - Department of General Surgery, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, China E-mail : [changhong@sdu.edu.cn](mailto:changhong@sdu.edu.cn).

**RESUMEN / SUMMARY:** - Hepatocellular carcinoma (HCC) is one of the most common malignancies, with a very poor prognosis. Despite significant improvements in diagnosis and treatment in recent years, the long-term therapeutic efficacy is poor, partially due to tumor metastasis, recurrence, and resistance to chemo- or radio-therapy. Recently, it was found that a major feature of tumors is a combination of unrestrained cell proliferation and impaired apoptosis. There are now 8 recognized members of the IAP-family: NAIP, c-IAP1, c-IAP2, XIAP, Survivin, Bruce, Livin and ILP-2. These proteins all contribute to inhibition of apoptosis, and provide new potential avenues of cancer treatment. As a powerful tool to suppress gene expression in mammalian cells, RNAi species for inhibiting IAP genes can be directed against cancers. This review will provide a brief introduction to recent developments of the application IAP-siRNA in tumor studies, with the aim of inspiring future treatment of HCC.

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[996]

**TÍTULO / TITLE:** - Ardipusilloside I induces apoptosis by regulating Bcl-2 family proteins in human mucoepidermoid carcinoma Mc3 cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - BMC Complement Altern Med. 2013 Nov 21;13(1):322.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1472-6882-13-322](#)

**AUTORES / AUTHORS:** - Xu XF; Zhang TL; Jin S; Rong W; Xiao X; Zhang WD; Wang PY; Wang XJ

**RESUMEN / SUMMARY:** - BACKGROUND: Ardisia pusilla A. DC., family Myrsinaceae, is a traditional Chinese medicine named Jiu Jie Long with a variety of pharmacological functions including anti-cancer activities. In this study, we purified a natural triterpenoid saponin, ardipusilloside I, from Ardisia pusilla, and show that it exhibits inhibitory activities in human mucoepidermoid carcinoma Mc3 cells. We also investigated the underlying mechanisms of proliferation inhibition that ardipusilloside I exerts on Mc3 cells. METHODS: MTT test was used to detect cell proliferation. Cell apoptosis was detected by transmission electron microscopy, Hoechst-33342 staining, DNA fragmentation detection, and flow cytometry. We also used western blot analysis to detect the potential mechanisms of apoptosis. RESULTS: Ardipusilloside I affected the viability of Mc3 cells in a dose- and time-dependent manner. The IC50 of ardipusilloside I was approximately 9.98 µg/ml at 48 h of treatment. Characteristic morphological changes of apoptosis, including nuclear condensation, boundary aggregation and splitting, and DNA fragmentation, were seen after treatment with 10 µg/ml ardipusilloside I for 48 h. Western blots demonstrated that ardipusilloside I caused Mc3 cell death through the induction of apoptosis by downregulation of Bcl-2

protein levels and upregulation of Bax and caspase-3 protein levels. CONCLUSIONS: Our results revealed that ardisinolide I could be a new active substance for mucoepidermoid carcinoma treatment. We demonstrated that the potential mechanism of inhibition might be through the induction of apoptosis by regulation of Bcl-2 family protein levels. This suggests a further rationale for the development of ardisinolide I as an anti-cancer agent.

[997]

**TÍTULO / TITLE:** - Combination of gene expression and genome copy number alteration has a prognostic value for breast cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Conf Proc IEEE Eng Med Biol Soc. 2013 Jul;2013:608-11. doi: 10.1109/EMBC.2013.6609573.

●● Enlace al texto completo (gratis o de pago) [1109/EMBC.2013.6609573](#)

**AUTORES / AUTHORS:** - Cava C; Zoppis I; Mauri G; Ripamonti M; Gallivanone F; Salvatore C; Gilardi MC; Castiglioni I

**RESUMEN / SUMMARY:** - Specific genome copy number alterations, such as deletions and amplifications are an important factor in tumor development and progression, and are also associated with changes in gene expression. By combining analyses of gene expression and genome copy number we identified genes as candidate biomarkers of BC which were validated as prognostic factors of the disease progression. These results suggest that the proposed combined approach may become a valuable method for BC prognosis.

[998]

**TÍTULO / TITLE:** - Cordycepin Regulates GSK-3beta/beta-Catenin Signaling in Human Leukemia Cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - PLoS One. 2013 Sep 26;8(9):e76320. doi: 10.1371/journal.pone.0076320.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0076320](#)

**AUTORES / AUTHORS:** - Ko BS; Lu YJ; Yao WL; Liu TA; Tzean SS; Shen TL; Liou JY  
**INSTITUCIÓN / INSTITUTION:** - Institute of Cellular and System Medicine, National Health Research Institutes, Zhunan, Taiwan ; Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

**RESUMEN / SUMMARY:** - BACKGROUND: Leukemia stem cells (LSCs) are a limitless cell source for the initiation and maintenance of leukemia. Activation of the Wnt/beta-catenin pathway is required for the survival and development of LSCs. Therefore, targeting beta-catenin is considered a therapeutic strategy for the treatment of leukemia. The goal of this study was to explore whether cordycepin, an active component of the traditional medicine Cordyceps sinensis, regulates beta-catenin expression in leukemia cells. METHODOLOGY AND PRINCIPAL FINDINGS: In this study, we found that cordycepin significantly suppressed cell proliferation in all malignant cancer cells, including U937, K562, A549, HepG2, SK-Hep1 and MCF7 in a dose-dependent manner. However, cordycepin reduced beta-catenin levels in U937, K562 and THP1 leukemia cells and had no effect on other solid cancer cells. In addition, treatment with cordycepin significantly suppressed leukemia colony formation in soft agar assay. Cordycepin enhanced proteasome-dependent degradation and

inhibited nuclear translocation of beta-catenin in leukemia cells. Cordycepin-reduced beta-catenin stability was restored by the addition of a pharmacological inhibitor of GSK-3beta, indicating that cordycepin-suppressed beta-catenin stability is mediated by the activation of GSK-3beta. Furthermore, cordycepin abolished the effect of Wnt3a-induced beta-catenin in leukemia cells. In addition, cordycepin-impaired beta-catenin is regulated by Akt activation but is not significantly influenced by AMPK or mTOR signal pathways. SIGNIFICANCE: Our findings show for the first time that cordycepin selectively reduces beta-catenin stability in leukemia but not in other solid tumor cells. This suppressive effect is mediated by regulating GSK-3beta. A synergistic combination of cordycepin with other treatments should be used as a novel strategy to eradicate leukemia via elimination of LSCs.

[999]

**TÍTULO / TITLE:** - Apoptosis of bladder transitional cell carcinoma T24 cells induced by adenovirus-mediated inducible nitric oxide synthase gene transfection.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Chin J Cancer Res. 2013 Oct;25(5):593-599.

●● Enlace al texto completo (gratis o de pago) [3978/j.issn.1000-9604.2013.10.11](#)

**AUTORES / AUTHORS:** - Tan J; Zeng Q; Jiang XZ; He LY; Wang JR; Yao K; Wang CH

**INSTITUCIÓN / INSTITUTION:** - Department of Urology, The Third Xiangya Hospital of Central South University, Department of Urology, The Third Xiangya Hospital, Yue-lu District, Changsha 410013, Hunan, China.

**RESUMEN / SUMMARY:** - OBJECTIVES: To investigate the effects of adenovirus-mediated inducible nitric oxide synthase gene transfection on bladder transitional cell carcinoma T24 cells, and to provide novel insights and approaches to clinical therapies against bladder transitional cell carcinoma. METHODS: Firstly, construct recombinant adenovirus vector pAd-iNOS of iNOS, followed by transfection of pAd-iNOS into HECK293 packaging cells. Thirdly, harvest recombinant adenovirus rAd-iNOS after amplification and purification procedures. Finally, transfect the recombinant adenovirus rAd-iNOS into human bladder carcinoma T24 cells and examine the effect of rAd-iNOS transfection on apoptosis of T24 and possible mechanism. RESULTS: As shown by this study, the recombinant adenovirus rAd-iNOS was constructed successfully. The virus titer was  $5.8 \times 10^8$  PFU/mL and recombinant was verified by PCR analysis. Transfection of adenovirus rAd-iNOS into T24 cells could induce secretion of high NO concentration, P53 protein expression up-regulation, as well as promotion of T24 cell apoptosis. CONCLUSIONS: The transfection of human bladder carcinoma T24 cells from recombinant adenovirus rAd-iNOS was confirmed to induce intracellular iNOS over-expression, high production of NO, up-regulation of intracellular P53 expression and promotion of cell apoptosis.

[1000]

**TÍTULO / TITLE:** - Soy soluble polysaccharide induces apoptosis in HCT116 human colon cancer cells via reactive oxygen species generation.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** - Mol Med Rep. 2013 Dec;8(6):1767-72. doi: 10.3892/mmr.2013.1725. Epub 2013 Oct 14.

●● Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1725](#)

**AUTORES / AUTHORS:** - Ko YJ; Jeong JW; Choi YH; Ryu CH

**INSTITUCIÓN / INSTITUTION:** - Division of Applied Life Sciences (BK 21 plus program), Institute of Agriculture and Life Sciences, Gyeongsang National University, Jinju, South Gyeongsang 660701, Republic of Korea.

**RESUMEN / SUMMARY:** - Previous studies have suggested that soy sauce contains specific bioactive components and various biological activities of soy sauce have been observed. Soy soluble polysaccharide (SSPS), a predominant bioactive compound in soy sauce, has numerous pharmacological actions, including antiinflammatory and immunomodulating activities. In the current study, the apoptotic effects of SSPS were investigated in HCT116 human colon cancer cells. Treatment with SSPS significantly inhibited cell growth in a concentrationdependent manner by inducing apoptosis but not necrosis. This induction was associated with the generation of reactive oxygen species (ROS), mitochondrial dysfunction, activation of caspases and cleavage of the poly (ADPribose) polymerase protein. Induction of apoptotic cell death of HCT116 cells by SSPS showed a correlation with the downregulation of members of the inhibitor of apoptosis protein family, including Xlinked inhibitor of apoptosis protein and antiapoptotic Bcl2, and upregulation of Bax and Bad. Administration of NacetylLcysteine, a scavenger of ROS, significantly decreased SSPSinduced apoptosis. These results indicate a critical role of signaling cascades involving a ROSmediated caspase pathway in the anticancer effects of SSPS.

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